Objective measures of cough severity

Lee, Kai Kong

Awarding institution:
King's College London

Objective measures of cough severity

Thesis submitted for the degree of

Doctor of Medicine

Kai Kong Lee

King's College London School of Medicine

2014

"Love and a cough cannot be hid"

George Herbert

Author's declaration

I declare that I am the author of this thesis and that the work is original. The data was acquired whilst working in the research laboratory at King's College Hospital between 2010 and 2012. I acquired all measurements myself. Access to the patients was facilitated by collaboration with Dr Surinder Birring at King's College Hospital and Ms Caroline Djema at The Corner Surgery. The distribution and set up of cough monitoring equipment for some patients was performed by the lung function staff at King's College Hospital under the guidance of Ms Tracey Fleming, Ms Claire Wood, and Ms Lynn Morgan. Dr Sergio Matos offered technical advice and wrote a custom script for MATLAB software for the purpose of cough sound analysis. Some of the figures were taken from the public domain and these are duly acknowledged within the legends.

Abstract

Cough is a common complaint that results in significant morbidity and impairment in quality of life. The assessment of cough severity is central to the diagnosis and clinical management of cough. The aim of this thesis was to evaluate objective measures of cough frequency and cough intensity in patients with acute and chronic cough.

24-hour cough frequency was investigated in a longitudinal observational study of 33 healthy subjects with acute cough. At baseline, 24-hour cough frequency was elevated and was associated with impaired health related quality of life. Cough frequency improved significantly over the 8-day study period. The minimal clinically important difference in cough frequency was determined as a 54% change from baseline. The sample sizes required for clinical trials to use cough frequency as a primary endpoint were calculated using this data. A second study of cough frequency was undertaken in 100 patients with chronic cough to investigate whether short duration recordings (1-6 hours) were comparable to 24-hours. Cough frequency obtained from short recordings were strongly correlated with 24-hour cough frequency (ρ=0.77 to 0.93), but those less than 4 hours were limited by weak relationships with subjective measures of cough. 4-hour cough frequency was found to be responsive to improvements in cough severity following trials of therapy, supporting its feasibility as a tool for assessing outcomes in chronic cough.

The intensity of cough is an important determinant of global cough severity, but few studies have assessed cough intensity objectively in patients with chronic cough. The intensity of voluntary, induced and spontaneous cough was investigated in 28 patients with chronic cough and 21 healthy controls. Oesophageal pressure (P_{oes}), gastric pressure (P_{ga}) and peak cough flow rate (PCFR) during maximum voluntary cough were significantly greater in patients with chronic cough compared with controls when taking into account the preceding inspired volume. There was no difference in expiratory muscle strength or degree of abdominal muscle activation between patients and controls but the compression phase duration (CPD) was increased in female patients with cough compared to controls (mean ± SD CPD 0.50

± 0.22 vs. 0.28 ± 0.17 seconds; p=0.007). Cough intensity during spontaneous cough was comparable to induced cough, but less than maximum voluntary cough intensity. P_{oes}, P_{ga} and PCFR were closely correlated with cough intensity visual analogue score (ρ=0.86 to 0.90), suggesting that these indices are important to subjective perception of cough intensity. Cough sound is a potential measure of cough intensity, but it has not been validated against physiological measures of cough intensity. The relationship between a range of cough sound parameters and PCFR and P_{oes} were investigated in 17 patients with chronic cough and 15 healthy controls. Cough sound power and energy were found to correlate most strongly with PCFR (ρ=0.82 to 0.88) and P_{oes} (ρ=0.85 to 0.89). The relationships between sound and PCFR or P_{oes} were similar for sound analysed from a fixed 0.5-second time-window and from time-windows that were manually marked by cough phase, supporting the potential for future automated analysis. Sound power and energy were highly repeatable measures (ICC 0.93 to 0.94). Cough sound measurement has the advantage of being non-invasive and suitable for ambulatory monitoring and further studies should now assess its responsiveness as a measure of cough intensity.

Publications arising from the thesis

1. **Lee KK**, Matos S, Evans DH, White P, Pavord ID, Birring SS. A longitudinal assessment of acute cough. American Journal of Respiratory and Critical Care Medicine 2013;187(9):991-997

2. **Lee KK**, Savani A, Matos S, Evans DH, Pavord ID, Birring SS. Four-hour cough frequency monitoring in chronic cough. Chest 2012;142(5):1237-1243

3. **Lee KK**, Birring SS. Cough. Medicine 2012; 40:173-176

4. **Lee KK**, Birring SS. Cough and sleep. Lung 2010; 188(0):91-94

Conference presentations

1. Cough intensity in voluntary, induced and spontaneous cough
   Lee KK, Ward K, Raywood E, Moxham J, Rafferty GF, Birring SS.
   Poster presentation at BTS Winter Meeting 2012, London

2. Cough sound intensity: the development of a novel measure of cough severity
   Lee KK, Matos S, Ward K, Raywood E, Evans DH, Moxham J, Rafferty GF, Birring SS.
   Poster presentation at BTS Winter Meeting 2012, London

3. Increased cough intensity in patients with chronic cough
   Lee KK, Ward K, Raywood E, Moxham J, Rafferty GF, Birring SS.
   Poster presentation at BTS Winter Meeting 2012, London

4. Changes in cough frequency, cough severity and quality of life in acute cough
   Lee KK, Matos S, Evans DH, Pavord ID, Birring SS.
   Poster presentation at ATS Conference 2012, San Francisco

5. Repeatability of cough frequency monitoring in acute cough
   Lee KK, Matos S, Evans DH, Pavord ID, Birring SS.
   Poster presentation at ATS Conference 2012, San Francisco

6. Acute cough: an observational longitudinal study
   Lee KK, Matos S, Evans DH, Pavord ID, Birring SS.
   Oral presentation at BTS Winter Meeting 2011, London

7. Predictors of 24-hour cough frequency in acute cough
   Lee KK, Matos S, Evans DH, Pavord ID, Birring SS.
   Oral presentation at BTS Winter Meeting 2011, London

8. Maximum cough pressures are increased in patients with chronic cough
   Lee KK, Ward K, Rafferty GF, Moxham J, Birring SS.
   Poster presentation at ERS Congress 2011, Amsterdam.

9. 4-hour cough frequency monitoring with the Leicester Cough Monitor
   Lee KK, Savani A, Matos S, Woods C, Pavord ID, Birring SS.
   Oral presentation at BTS Winter Meeting 2010, London.

10. Short term oral corticosteroid trials in patients with unexplained chronic cough
    Lee KK, Savani A, Patel AS, Wood C, Morgan L, Fleming T, Pavord ID, Birring SS.
    Poster presentation at ERS Congress 2010, Barcelona.

TABLE OF CONTENTS

Table of Figures

Index of Tables

1 Introduction

1.1 Cough: the clinical problem

Cough is a natural defence mechanism that clears secretions from the airways and protects against aspiration of inhaled foreign bodies. An impaired cough reflex is seen in patients with conditions such as neuromuscular disease, stroke and Parkinson's disease and can lead to an increased risk of aspiration and pulmonary infections [1-4]. At the other end of the spectrum are patients with heightened cough reflex sensitivity who are troubled by excessive coughing. Cough can be acute and transient when due to upper respiratory tract infection but in some cases it can be chronic and without apparent physiological advantage for its persistence [5]. The symptom of cough is often perceived as a trivial problem, but it may be associated with significant physical and psychological morbidity. Syncope, urinary incontinence, chest pain, sleep disturbance, relationship difficulties, social embarrassment and depression are just some of the adverse consequences of chronic cough [6-10]. The assessment of the severity of cough is important since the clinical response to trials of therapy is central to establishing a diagnosis for chronic cough and evaluating the efficacy of antitussive therapy. A number of subjective tools have been developed and validated, particularly those that measure health status, but there is a relative paucity of studies for objective measures [11, 12]. A greater understanding of objective cough measures would facilitate better clinical assessment of patients and research in future.

1.1.1 Epidemiology

Cough is a common complaint. The prevalence of cough is estimated between 9-33% in the community and the economic cost to society is substantial; approximately £100 million is spent on antitussive drugs every year in the UK [13-15]. Most of this burden relates to acute cough due to viral upper respiratory tract infection (URTI), of which there are an estimated 48 million episodes per year in the UK [16]. On average, it is estimated that each adult is affected by URTI 2-5 times a year [17]. Chronic cough is also common, with a reported prevalence of 12% of the

general population in the UK, and accounts for 10% of all respiratory outpatient clinic referrals [16, 18].

1.1.2 Classification of cough

Cough is thought to be a manifesting symptom of a range of conditions. It is usually classified according to duration of presence. Acute cough is defined as a cough which lasts less than 3 weeks in duration, sub-acute cough as that lasting between 3 and 8 weeks, and chronic cough as that lasting greater than 8 weeks in duration [19]. Despite some degree of overlap, the potential aetiology of cough is often discernible from whether the cough is acute, sub-acute or chronic in nature.

1.1.3 Acute cough

Acute cough is a major problem and leads to disturbed sleep, time off work and significantly impaired quality of life [12, 20]. The cost to the UK economy is estimated at £979 million when considering healthcare costs, loss of productivity and costs of over-the-counter medications [16]. The economic impact in the USA approaches $40 billion [21].

Acute cough is most often due to viral upper respiratory tract infection [16, 22]. The mechanism for cough in URTI may be related to a transient increase in cough reflex sensitivity [5]. A recent study has demonstrated that cough receptor expression is up-regulated in neuronal cells infected with human rhinovirus [23].

Despite the fact that acute cough is usually self-limiting, patients still spend around £100 million on antitussive medications every year in the UK, and up to $3 billion in the USA [14, 24]. However, a recent Cochrane review failed to establish the efficacy of currently available over-the-counter antitussive remedies [25]. It was reported that the studies were limited by a lack of validated outcomes measures and objective tools, resulting in unclear clinical significance of the results [25]. There is a need for greater understanding of the course and degree of natural recovery of acute cough using validated outcome measures in order to advance knowledge of the condition and facilitate the design of future clinical trials of antitussive drugs [26].

1.1.4 Sub-acute cough

Sub-acute cough is usually attributed to post-infectious cough. Suggested definition criteria, other than a duration lasting between three and eight weeks, includes the absence of pneumonia, a normal chest radiograph and the eventual resolution of the cough [27]. If the clinical picture is not suggestive of post-infectious cough, then workup for chronic cough is recommended.

It is speculated the mechanism responsible for post-infectious cough is of transient inflammation of the lower airways with possible further aggravation by either bronchial hyper-responsiveness, mucus hyper-secretion, precipitation of pre-existing gastro-oesophageal reflux or a combination of these [27].

Treatment may not be required since post-infectious cough is self-limiting. Inhaled ipratropium or a short course of inhaled or oral corticosteroids are often considered when the cough is troublesome but the evidence base is weak [28]. Antibiotics are not usually recommended unless Bordatella pertussis, the prevalence of which has risen to its highest level in the last decade, is suspected as the cause [27, 29].

1.1.5 Chronic cough

Chronic cough can be a manifestation of, or be associated with, many conditions. The list is long and varied but some of the recognised associations are given in Table 1-1. Most of these conditions are evident following initial clinical assessment, spirometry and chest radiography. The remainder of cases are often referred to respiratory physicians and specialist cough clinics for further investigation. These patients tend to be non-smokers with unremarkable clinical examination and normal lung function. This cohort is generally the population of interest in chronic cough studies. Several specialist cough centres have conducted prevalence studies on the associated causes of chronic cough (Table 1-2). The conditions most commonly associated with cough are asthma, gastro-oesophageal reflux disease and rhinitis. In 1981, Irwin et al proposed an "anatomical diagnostic protocol" for investigating patients based on the evaluation for these common associations, and has been the basis for clinical guidelines for the past 30 years - this is described in more detail in section 1.1.6 [30].

Table 1-1 Conditions associated with chronic cough in presence of a normal chest x-ray

Asthma
Gastro-oesophageal reflux
Rhinosinusitis
Eosinophilic bronchitis
Ace-inhibitor drug therapy
Obstructive sleep apnoea
Tonsillar enlargement
Snoring
Premature ventricular complexes
Organ-specific auto-immune disease
Ear wax (Arnold's reflex)

Table 1-2 Causes of cough in specialist respiratory and cough clinics

	Number (women)	Diagnosis			
		Asthma/CVA/EB/AC	GORD	PNDS	Idiopathic
USA					
Irwin [31]	102 (59)	24%	21%	41%	1%
Poe [32]	139 (84)	33% (mostly CVA)	5%	27%	12%
Smyrnios [33]	71 (32)	24%	15%	40%	3%
Mello [34]	88 (64)	14%	40%	38%	2%
French [9]	39 (32)	15%	36%	40%	3%
UK					
McGarvey [35]	43 (29)	35% (CVA)	19%	35%	19%
Brightling [36]	91 (NR)	31% (EB 13%)	8%	24%	7%
Birring [37]	236 (NR)	24%	15%	12%	26%
Niimi [38]	50 (39)	30%	11%	13%	40%
Kastelik [39]	131 (86)	24%	22%	6%	7%
Japan					
Fujimura [40]	176 (NR)	79%	4%	26%	6%
Shirahata [41]	55 (NR)	42% (CVA)	0	7%	13%
Brazil					
Palombini [42]	78 (51)	59%	41%	58%	0%

CVA: cough variant asthma; EB: eosinophilic bronchitis; AC: atopic cough; GORD: gastro-oesophageal reflux disease; PNDS: postnasal drip syndrome; NR: not recorded.

Cough Variant Asthma

Cough can be the sole clinical manifestation of asthma and this is often referred to as cough variant asthma (CVA). CVA is a common cause of cough, accounting for around 30% of cases of cough referred to specialist clinics (Table 1-2). Originally described by Glauser in 1972 and more clearly defined 7 years later by Corrao, CVA is typified by the presence of dry cough and demonstrable airway hyper-responsiveness but without airflow obstruction on spirometry [43, 44].

The mechanism of cough is likely to be one or more of eosinophilic airway inflammation, airway hyper-responsiveness and cough reflex hypersensitivity [45]. Indeed, the airway inflammation seen in CVA is similar to that of classic asthma, with similar eosinophilia levels in bronchial biopsies and bronchoalveolar lavage [46]. Airway remodelling occurs in CVA, but to a lesser extent than in classic asthma [47]. Unlike classic asthma however, patients with CVA have a more heightened cough reflex when assessed by cough challenge tests [48].

The characteristics of the cough and presence of nocturnal cough are not helpful in distinguishing CVA from other causes of cough. Routine tests for asthma such as peak flow monitoring, bronchodilator reversibility and bronchoprovocation tests have a limited role in the assessment of CVA since they lack sensitivity and specificity for the diagnosis and are poor at predicting the response to treatment [49, 50]. Measures of airway inflammation such as induced sputum eosinophil differential cell count (>3%) or fraction of exhaled nitric oxide (FeNO) are better tests but are seldom available to physicians in current clinical practice [49, 51]. Diagnosis by trial of therapy is therefore widely employed. Inhaled corticosteroids are effective for CVA and are often used for this purpose [52-54]. In cases where concerns exist regarding inhaler technique and compliance, a trial of oral corticosteroid is recommended [16, 52].

Treatment with inhaled bronchodilator therapy has been shown to reduce subjective cough severity but not objective cough counts, leading to opinion that its efficacy needs to be re-evaluated in larger randomised controlled trials [52, 55]. Leukotriene receptor antagonists have been shown to improve subjective cough

scores and cough reflex sensitivity and are a further option [56]. In most patients with CVA, the cough returns following cessation of therapy and follow-up studies suggest nearly 30% of patients can go on to develop symptoms of classic asthma [57].

Eosinophilic bronchitis

Eosinophilic bronchitis (EB) was first described by Gibson et al in 1989 when they identified a group of patients with corticosteroid responsive cough who all had eosinophilic sputum infiltration but without reversible airflow obstruction or the symptoms associated with asthma [58]. These patients were non-smokers and were distinguishable from patients with chronic bronchitis [59]. Like CVA and classic asthma, EB is characterised by eosinophilic airway inflammation. In contrast to CVA and asthma however, airway hyper-responsiveness is absent [58, 60]. The lack of disordered airway function in EB is thought to be due to the absence of mast cell inflammation in airway smooth muscle that is usually seen in asthma [61].

EB accounts for up to 10-13% of chronic cough referrals to respiratory clinics and may co-exist with other airway diseases such as COPD [36, 62]. The diagnosis may be established by the demonstration of eosinophilic airway inflammation in induced sputum or exhaled nitric oxide measurement in the absence of airway hyper-responsiveness [36]. Inhaled corticosteroids are effective at reducing cough reflex hypersensitivity and cough severity [60]. EB is seldom diagnosed outside of specialist clinics, probably due to the combination of lack of access to the diagnostic tests and mistaken diagnosis of classic asthma following successful response to corticosteroids [36, 52].

Atopic cough is a condition that has been reported almost exclusively in Japan. It is characterised by chronic cough in the presence of atopy but without airway hyper-responsiveness and bronchodilator reversibility. Atopy is confirmed by positive sputum eosinophilic airway inflammation, elevated total IgE level, positive allergen skin prick testing or elevated specific IgE [57]. Atopic cough differs from EB in that

there is no bronchoalveolar lavage eosinophilia but in most other regards, it is analogous to EB [63].

Gastro-oesophageal reflux related cough

In 1977, a systematic review of patients with chronic cough by Irwin and colleagues reported a high prevalence of symptoms of gastro-oesophageal reflux (GOR) in patients with chronic cough and led to the widespread practice of evaluating for and treating extra-pulmonary symptoms [64]. Since then, GOR has been found to account for up to 41% of chronic cough in patients referred to specialist clinics (Table 1-2).

Suggested mechanisms for cough in GOR include the microaspiration of refluxate into the trachea-bronchial tree (the reflux theory) or vagal stimulation of the oesophageal-bronchial reflex (the reflex theory) [65, 66]. The latter is supported by the fact that cough can be induced by infusing acid into the distal oesophagus [67].

Recent randomised controlled trials have failed to confirm the positive findings of earlier uncontrolled studies on the efficacy of proton-pump inhibitors (PPI) for improving cough in patients with GOR related cough [68-70]. Subjective cough scores were used to define response in those trials and the inconsistency between results could be due to lack of objective outcome measures. Furthermore, the early trials were uncontrolled or small in number. As a result, the role of acid GOR in chronic cough has been questioned [52]. Only a minority of reflux events reach the proximal oesophagus in GOR related cough, which suggests that a central neuronal process may be the more likely mechanism for the sensitisation of the oesophageal-bronchial reflex than peripheral microaspiration [71, 72].

The symptom association probability (SAP) index can be used to define whether cough events and reflux events are temporally related more than that which would occur by chance. In a study of patients with chronic cough by Blondeau et al, where asthma and rhinitis had been excluded, only 1-9% of subjects had a positive SAP score for acid reflux and cough [71]. Cough events were recorded both subjectively

on a data logger and objectively by analysis of manometric changes in the oesophageal impedance pH recording. The lower SAP rate (1%) was found when relating reflux events to subjectively recorded coughs and the higher rate (9%) was found with manometric labelled cough. The poor correlation between subjective cough scores and objective cough frequency is well documented and the use of manometric cough labelling alone could lead to inaccuracies since actions such as gag or sneezes can mimic cough on manometry [73]. The study was recently repeated by Smith et al using a sound based objective cough frequency monitor to detect cough events [72]. A higher positive SAP rate (31%) was found in their study, which highlights the potential differences with use of objective cough detection tools.

Non-acid GOR has been postulated to be more important than acid GOR in reflux related cough [74]. In the study by Blondeau et al, a positive SAP for non-acid reflux was found in 9-23% of patients compared with 1-9% for acid-related reflux [71]. In the study by Smith et al, the SAP positive rate for non-acid reflux was identical to that for acid reflux (31%) [72]. Non-acid reflux events have not been shown to occur any more frequently in chronic cough when compared with healthy controls [75].

Pharmacological therapy for non-acid GOR associated cough includes alginates and motility agents, such as metoclopramide and domperidone, but evidence from controlled trials to support their use is currently lacking [52].

There is also uncertainty in the role of investigations for GOR related cough. Oesophageal pH monitoring may detect reflux events but are poor at predicting response to anti-reflux therapy [76]. At present, there is no evidence that tests for non-acid GOR, such as oesophageal impedance monitoring, are able to predict the response to treatment.

The current evidence for surgical therapy for cough associated with GOR, Nissen fundoplication, is also weak and this procedure is associated with significant adverse symptoms and complications [52, 77]. The need for controlled studies using objective outcomes has recently been re-emphasised [66].

Rhinosinusitis

Rhinosinusitis, also referred to as post-nasal drip syndrome or upper airways cough syndrome (UACS), has been reported in up to 58% of patients with chronic cough [42]. As with GOR, there is a paucity of evidence to support a causal role of rhinitis in cough. Ear, nose and throat specialist evaluation and laryngoscopy is worthwhile particularly when upper airway symptoms are prominent but X-ray and CT scan of the sinuses are poorly predictive of the response to treatment and are not recommended for routine use [78]. Empirical treatment is recommended before diagnostic workup since the response to treatment is key to establishing the diagnosis. Anti-histamines, decongestants and topical nasal corticosteroids are available treatments.

1.1.6 Evaluation and treatment of the patient with cough

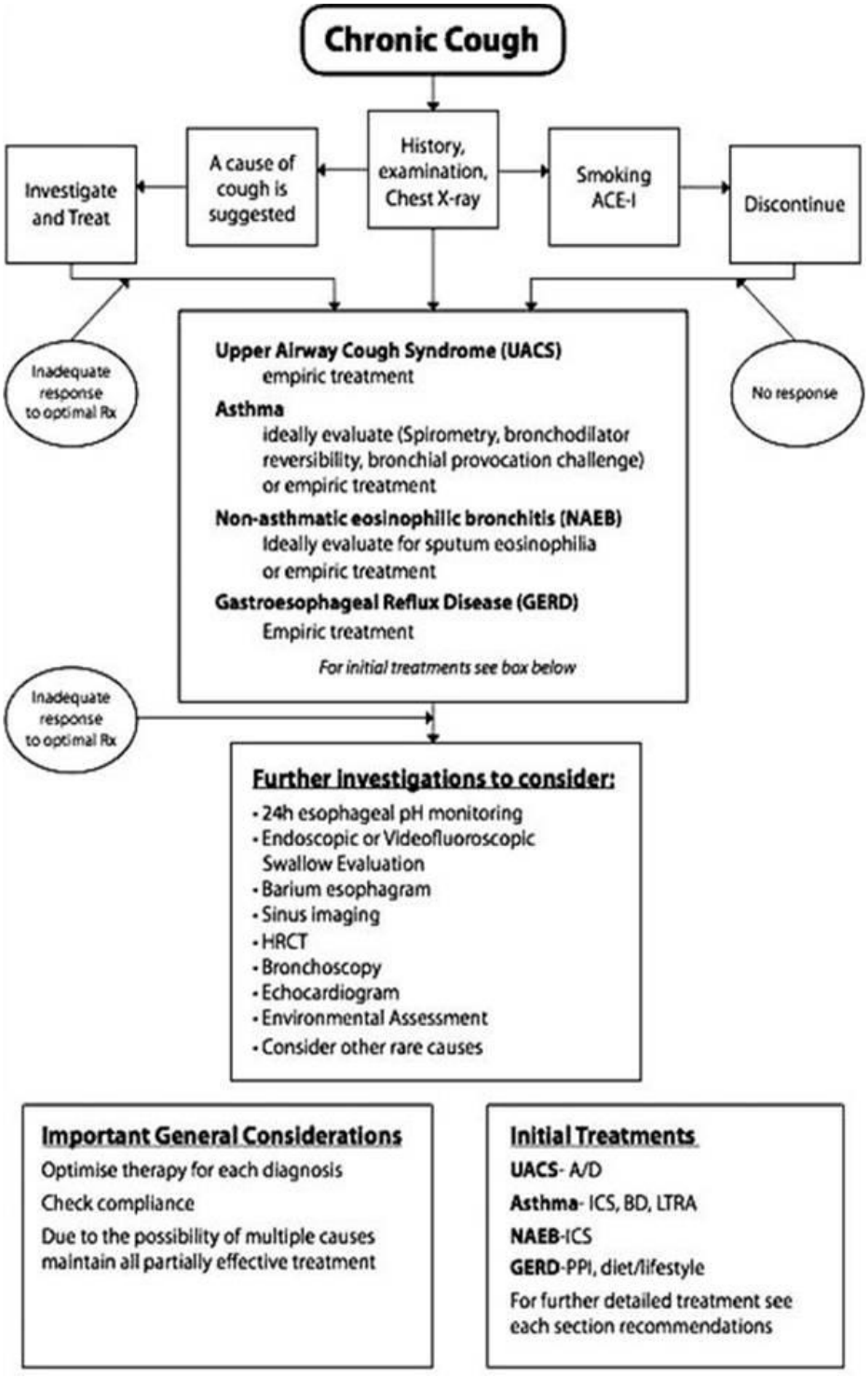
Current guidelines on the assessment of the patient with cough are based on the anatomical diagnostic protocol approach proposed by Irwin et al [16, 30, 78, 79]. This approach involves targeting likely causes of cough by identifying symptoms or signs that pinpoint the likely anatomical origin of the associated condition (i.e. heartburn suggesting gastro-oesophageal reflux disease as the cause of cough). Therapeutic trials are endorsed, in addition to careful history, examination, spirometry and a chest x-ray. The required specific treatment may be apparent from the initial assessment, but empirical therapy may also be necessary. An example of a diagnostic and management protocol is presented in Figure 1-1.

Treatment of cough is often integrated into the evaluation process since trials of therapy are often employed to establish the diagnosis. The specific treatments for cough have been briefly outlined in the earlier sections on cough aetiology. Resolution of cough with specific therapy confirms the diagnosis. On the other hand, lack of response to therapy can cause uncertainty since it may result from a genuine lack of treatment efficacy or incorrect diagnosis.

Many cases of chronic cough remain unexplained despite detailed investigation. This is reported to account for up to 42% of patients referred for investigation [80]. A number of terms are used in the literature to describe the cough in this cohort: idiopathic, refractory, sensory neuropathic, laryngeal sensory neuropathy, airway sensory hyper-reactivity and vagal neuropathy-associated cough. These patients are predominantly female and middle aged [80]. An onset following viral illness and an association with organ specific autoimmune disease has been described in some patients [80-82]. This group have demonstrable heightened cough reflex sensitivity, and this has led some investigators to propose a greater focus on that key underlying mechanism and the use of a new name "Cough Hypersensitivity Syndrome" (CHS) to type these patients [45, 52, 83]. An approach for the evaluation of cough based on features of cough hypersensitivity rather than the traditional anatomical protocol has been suggested [45, 84].

In cases of refractory cough, a limited number of non-specific treatments are available. Pharmacological agents include Morphine, which has been shown to suppress cough in a randomised double-blind placebo-controlled trial, but is associated with side effects [85]. Amitriptyline has been shown to be superior to other cough suppressants in a small open label study and gabapentin has also recently been reported to be efficacious in case reports and a recent randomised controlled trial [86-88]. Cough suppression therapy is a promising non-pharmacological treatment provided by speech therapists and physiotherapists which involves education, avoidance of triggers, vocal hygiene, correction of breathing patterns and cough control [89, 90]. Improvements in cough specific quality of life as well as voice, breathing and cough scores were demonstrated although randomised placebo-controlled trials are required to confirm the findings [89, 90].

Figure 1-1 Example of a diagnostic and management protocol



Reproduced from the American College of Chest Physicians cough guidelines [78]

1.2 The cough reflex

Cough is a vagally mediated physiological reflex that is designed to protect the lungs by preventing aspiration and clearing secretions or foreign material from the airways [91, 92]. It is a complex manoeuvre that requires intact sensory pathways from airway cough receptors, cortical processing and a functional efferent system from the brain to the appropriate muscles (Figure 1-2).

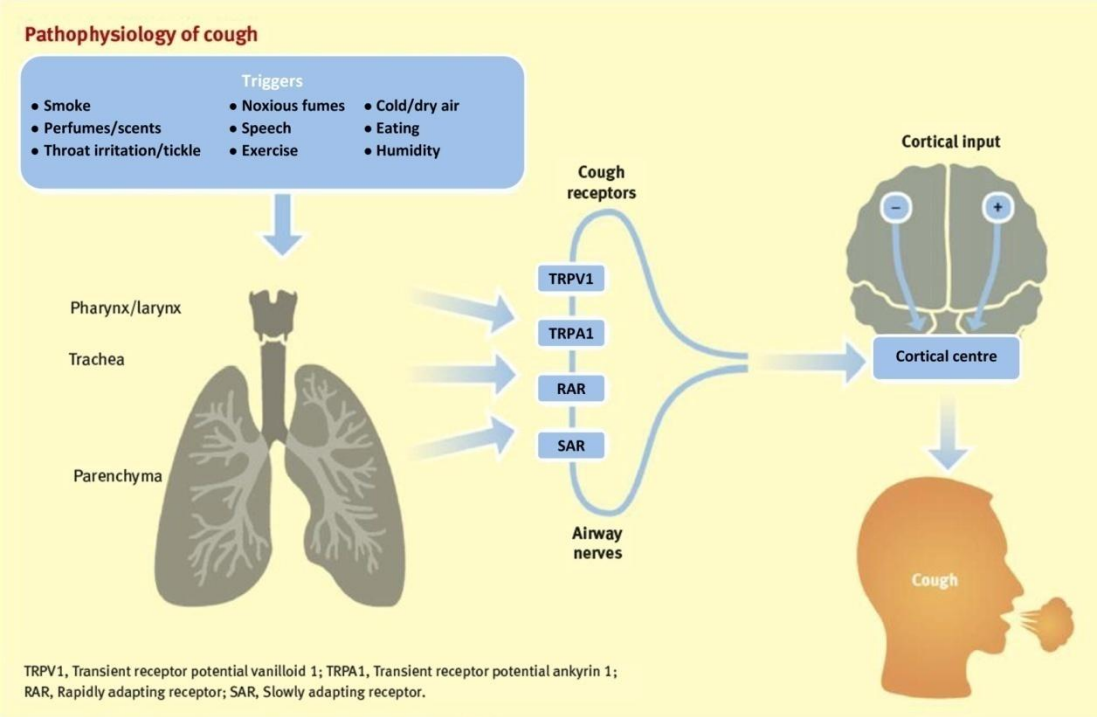
In this chapter, the physiology of cough will be described by reviewing the understanding of the afferent and efferent pathways. Most evidence has originated from animal models since it is difficult to conduct in vivo human studies for obvious reasons. Animal models are also necessary for the development of antitussive therapies [93]. The guinea pig cough model is felt to be the most representative of the induced cough response in humans, but it is acknowledged that differences in experimental settings and protocols can influence the relevance of these models to humans [93, 94]. The major limitation of animal models is the inability to study cough analogous to human spontaneous cough.

1.2.1 The afferent pathway

As a reflex defence mechanism, cough is initiated in response to peripheral stimulation of cough receptors. The brainstem coordinates inputs from peripheral afferent nerves and from central regulatory cortical fibres and then activates the motor pathway of the cough reflex (Figure 1-2) [13].

Cough receptors are most concentrated in the upper airways but are also found throughout the lower airways and lung parenchyma. A wide range of triggers can activate these receptors including cigarette smoke, capsaicin, acid and alkaline solutions, hypertonic saline and mechanical stimulation [13, 95]. In some patients however, no exogenous tussogenic trigger is identified, suggesting exaggerated sensation [96]. Indeed, patients with chronic cough often report coughing in response to otherwise banal activities such as speech, laughter and eating [96].

Figure 1-2 Overview of cough pathophysiology



TRPV1: transient receptor potential vanilloid cation channel subtype 1; TRPA1: transient receptor potential ankyrin cation channel subtype 1; RAR rapidly adapting receptor; SAR: slowly adapting receptor. Reproduced from Lee et al (2012) [84].

The receptors that mediate cough have not been conclusively identified, but they include Rapidly Adapting Receptors (RARs) and non-myelinated C-fibre receptors [97]. They differ with respect to conduction velocity and in their sensitivities to varied stimuli but both transmit their signals via the afferent vagus nerves [97]. RARs respond to excess mucus secretion and oedema, whereas C-fibres are sensitive to chemical stimuli such as capsaicin. Capsaicin binds to, and stimulates, TRPV1 receptors (transient receptor potential vanilloid subtype 1 ion channel). TRPV1 is the best known member of the TRP family and the subtype most implicated in cough [98]. Other subtypes include TRPA1 and TRPM8. TRPV1 receptors are located throughout the respiratory tract but have also been identified within the central nervous system, skin, gastrointestinal tract and nasal mucosa in animal models [99-102]. TRPV1 is also activated by acids, heat, and endogenous mediators such as bradykinin, substance P and prostaglandins [98]. TRPV1 receptor

activation leads to increased permeability to Na^+ and Ca^{2+} ions and the resulting influx causes neuronal depolarisation [103].

The vagal afferents from both C-fibres and RARs converge at the Nucleus Tractus Solitarius (NTS), which sends out impulses to the other relevant areas in the brainstem and then subsequent signalling via sympathetic nerves to stimulate the respiratory muscles to contract and produce a cough (Figure 1-2) [13]. During chronic cough, airway inflammation may cause neuroplastic changes, such as the up-regulation the TRPV1 receptors. This may increase the patient's susceptibility to coughing in response to trivial stimuli [13, 104].

Many patients with chronic cough report laryngeal paraesthesia, suggesting afferent nerve hypersensitisation as the underlying pathophysiological mechanism [96]. This cough reflex hypersensitivity is transient or reversible when associated with infection, eosinophilic airway inflammation and angiotensin-converting enzyme (ACE) inhibitor drug therapy, but in most patients with unexplained chronic cough it is persistent [52]. An enhanced cough reflex has been demonstrated in a number of conditions typically associated with cough [48]. The mechanism by which this sensitisation occurs remains poorly understood.

It is possible to assess or identify cough reflex hypersensitivity with cough challenge tests using tussive agents such as capsaicin but they are of limited value for clinical use since they cannot reliably discriminate subjects with cough from healthy subjects [48]. A better understanding of these cough mechanisms however has led to a shift away from historical anatomically based diagnostic 'causal' approach and towards one based on the pathophysiology mechanisms. Some have suggested that those conditions classically felt to be causing the cough are in fact acting as aggravating factors on underlying cough reflex hypersensitivity [45, 83]. Indeed, several of the current antitussive treatments in development are targeted against these over-sensitised cough receptors [105, 106]. There is still some uncertainty around cough hypersensitivity syndrome, due to the lack of an accepted definition, and it therefore remains to be seen how well this view will be received.

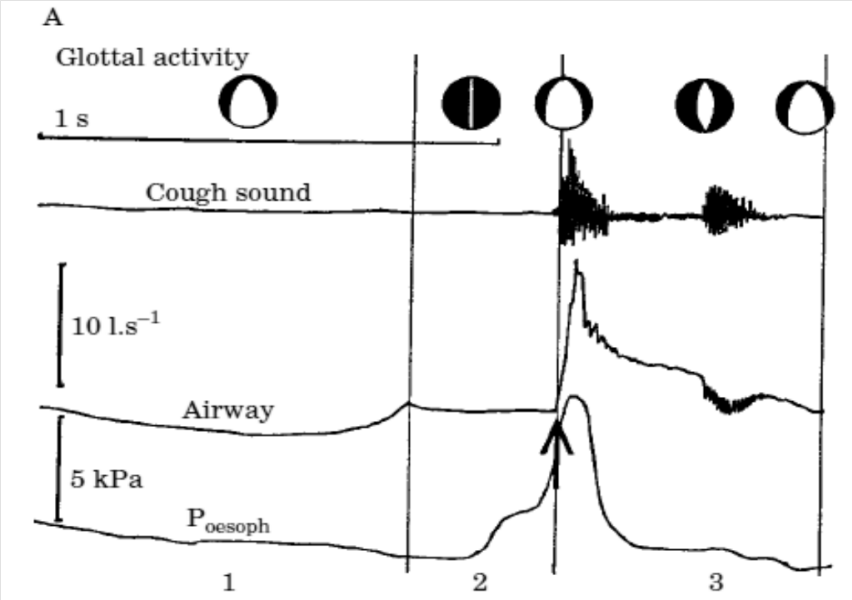
1.2.2 The cough motor system

In physiological terms, cough is described as an inspiration followed by a forced expiratory effort against a transiently closed glottis resulting in a rapid expulsion of air [107].

The inspiratory phase of the cough sequence has more importance than simply providing a volume of air that can be expelled to assist clearance of the airways. The expansion of the thorax also results in lengthening of the expiratory muscles, thereby optimising force generation due to the length-tension relationship of muscle fibres [108]. The result of inhalation to high lung volumes is that higher pressures can be generated by the muscles for any given degree of neural activation [109].

At the end of inspiration, the glottis closes, preventing escape of air and permitting retention of intra-thoracic pressure. While the glottis is closed, an active expiratory effort follows, raising the intra-abdominal and intra-thoracic pressures during this "compression phase" (Figure 1-3). Additionally, glottis closure also minimises shortening of the expiratory muscle fibres, which in turn encourages isometric contraction. This isometric state maximises efficiency of the contraction with a more optimal force-length relationship [110]. The glottis then opens while expiratory effort continues, leading to transmission of intra-thoracic pressure into thoracic airflow, which is labelled the cough expiratory phase. Airflow rate can vary throughout the expiratory phase but peak airflow usually occurs soon after glottic opening during an initial burst which lasts approximately 30-50 ms [109]. Peak airflow during these bursts can exceed maximal flow generated during voluntary expiratory flow manoeuvres [111, 112]. Supramaximal flows are possible due to the added effect of dynamic airway compression during cough [113]. Airstream velocity is inversely proportional to the cross-sectional area in which the flow is traversing and, therefore, dynamic compression will increase velocity [109]. The ability to generate supramaximal flow has been linked with expiratory muscle strength in patients with neuromuscular weakness [111, 114]. The importance of supramaximal flow on airway clearance is not clear [112]. Nevertheless, cough peak flow rate remains a widely used tool for quantifying cough function.

Figure 1-3 Glottis activity during cough



Reproduced from Korpas et al (1996) [115].

1.2.3 Supramedullary control of cough

The cough motor pathway is regulated by higher cortical control and is the subject of much interest. It is known that humans are able to both voluntarily produce and inhibit a cough manoeuvre [116, 117]. Reflex coughs can be inhibited by simply instructing subjects to consciously suppress their cough [116]. Similarly, subjects undergoing tussogenic cough challenge testing can perceive an urge to cough without an actual motor cough response, suggesting that subjects can voluntarily ignore the urge [118]. Finally, diurnal variation in cough frequency has been consistently demonstrated with significantly lower numbers of coughs occurring at night, implying an inhibitory effect of sleep on spontaneous cough, and reflex cough thresholds have been shown to be higher at night [119-121]. The exact level of the control in unclear, but is most likely to be cortical. This is supported by the demonstration that placebo can reduce cough [122].

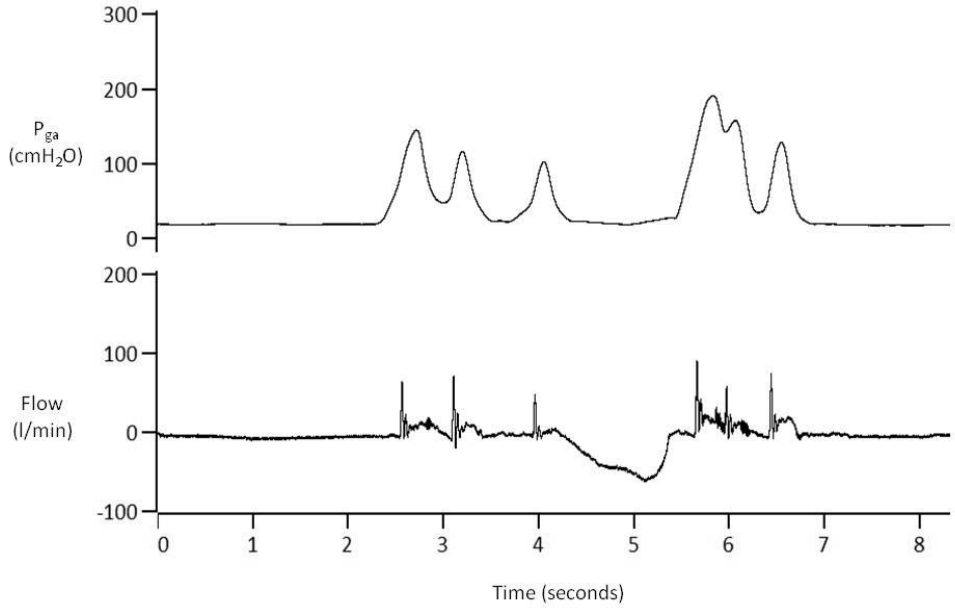
1.2.4 The expiratory reflex

The expiratory reflex (ER) is another respiratory reflex that is similar to cough but with one important difference. Although the efferent sequence also includes glottis closure and a forced expiratory effort like a cough reflex, there is no preceding inspiratory phase in ERs (Figure 1-4) [123]. Stimulation of the larynx by injection of distilled water or mechanical stimulation induces both expiratory reflexes and coughs [124].

The distinction between the two reflexes has been compared by Widdicombe and Fontana [107]. They note differences in brainstem neural pathways, modulatory actions, and pharmacological inhibitions between the two reflexes. The afferent pathways from the peripheral cough receptors to the cough centre for the two reflexes must be different, as one does not trigger an inspiration.

The lack of a preparatory inspiration during the ER could have major implications when considering the efficiency of the reflex as a defence mechanism. The volume of inspired air prior to coughing has been shown to correlate with peak cough flow rate, and hence a lack of inspiration could be detrimental to cough efficiency [125]. On the other hand, however, a lack of inspiratory action could be advantageous in the event of inhalation of foreign material from the larynx in order to prevent further propagation into the tracheobronchial tree. Other differences also exist between the ER and cough. In animal models, duration and intensity of abdominal muscle electromyographic activity (EMG) were reduced in ER compared with cough [126]. In the same study, laryngeal muscle EMG burst duration was also reduced in ER when compared with cough, although the EMG amplitude was higher in ER [126].

Figure 1-4 Pressure and flow changes during cough and expiratory reflex



Trace showing 3 expiratory reflexes (without preceding inspiration) followed by a cough and 2 further ERs during capsaicin cough challenge testing in a female healthy subject. Upper trace represents gastric pressure and lower trace represents airflow.

There is differing opinion on the classification of the ER as a separate entity. Whilst some would define the ER as a distinct reflex, others consider it merely a result of the stimulus to cough occurring at different phases of the respiratory cycle [127]. The ER has been studied in the laboratory using experimentally induced cough, either chemically or mechanically. To my knowledge, the ER has not been studied in patients with chronic cough or during spontaneous pathological cough.

Most cough studies have not defined which cough reflex was being assessed (true cough or ER, or more likely due to the lack of distinction, both). It is therefore unknown how much ER and cough contribute to spontaneous coughing in patients with chronic cough.

1.2.5 The muscles which contribute to cough

Early electromyographic studies confirmed upper and lower abdominal muscle activity during the expulsive phase of cough [128]. These muscles include the rectus abdominis, transversus abdominis, internal oblique and external oblique muscles [129, 130]. In addition, activity from the pectoralis major and latissimus dorsi has been demonstrated in tetraplegic and healthy subjects, suggesting that they can act as accessory expiratory muscles [131, 132]. If the initial inspiration phase of cough is included, then the diaphragm and other inspiratory muscles are also of importance.

The patterns of activation of the main and accessory expiratory muscles during voluntary and reflex cough were studied in healthy subjects by Lasserson et al [133]. During voluntary cough, predominantly the main expiratory muscles were activated at lower cough flow rates with sequential and increasing recruitment of accessory expiratory muscles at higher cough intensities. In induced cough, there was rapid and diffuse activation of both muscle groups, but with shorter EMG burst duration.

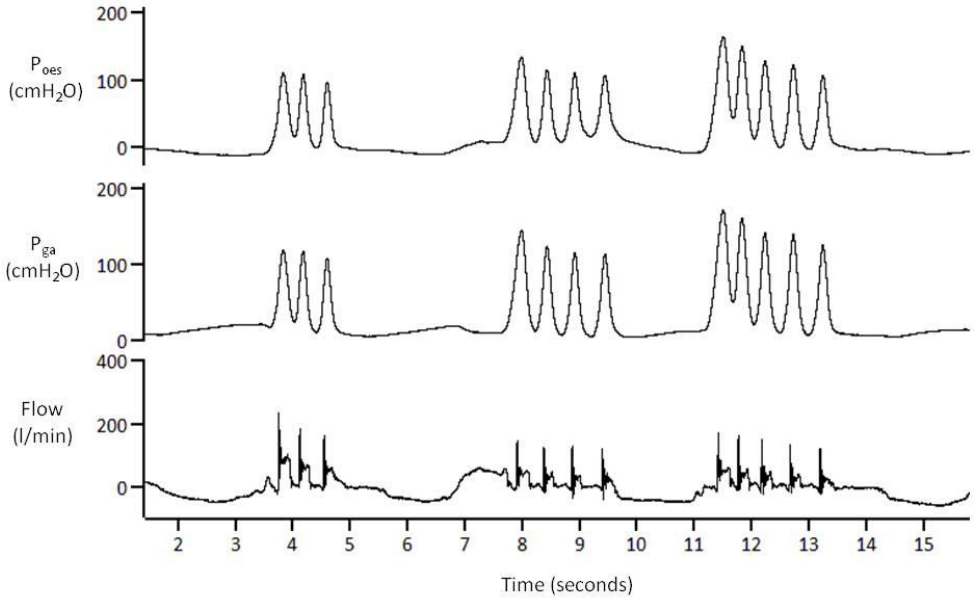
The laryngeal muscles are important for the compression phase of cough. Rapid vocal cord closure is required to allow build up of sub-glottic pressure [134]. Poletto et al demonstrated that thyroarytenoid and lateral cricoarytenoid EMG activity was related to vocal cord closure during voluntary cough in healthy subjects [134]. Posterior cricoarytenoid EMG activity correlated with opening of the vocal cords in cough but its activity was not specific to cough manoeuvres. Poliacek et al studied the relationship between laryngeal and respiratory muscle activity during cough in cats [126]. They found that thyroarytenoid and diaphragmatic activity was prolonged in response to laryngeal stimulation compared to tracheobronchial stimulation, but that abdominal muscle activity was no different between the two stimuli. A similar study has not been performed in humans.

1.2.6 Voluntary, induced and spontaneous cough

Spontaneous or pathological cough is of most significance since it is relevant to patients. However, the unpredictable timing of spontaneous cough in patients and the lack of it in healthy subjects has necessitated the study of experimental cough models such as voluntary cough or induced cough. Physiological differences

between induced and voluntary cough have been demonstrated [133, 135]. For example, as described earlier, voluntary cough is associated with sequential activation of the main expiratory muscles followed by activation of accessory muscles, whereas induced cough is associated with simultaneous activation of both muscle groups [133]. Addington et al found that intra-abdominal pressure remained elevated above baseline throughout induced coughs bouts, suggesting sustained expiratory effort [135]. Diaphragmatic movement during induced cough may also be greater than in voluntary cough [136]. Induced cough often results in bouts of coughing, which may be similar to spontaneous cough since patients with spontaneous cough often report coughing fits (Figure 1-5) [137, 138]. Coughs within bouts tend to be of shorter duration than single voluntary coughs, suggesting some modification to the motor pattern [125]. The experimental model that most closely represents spontaneous cough is unknown.

Figure 1-5 A series of cough bouts



3 bouts of coughing represented as numerous efforts occurring in close succession. Trace obtained during capsaicin cough challenge testing in a male patient with chronic cough. P_{oes}: oesophageal pressure; P_{ga}: gastric pressure; Flow: respiratory flow rate.

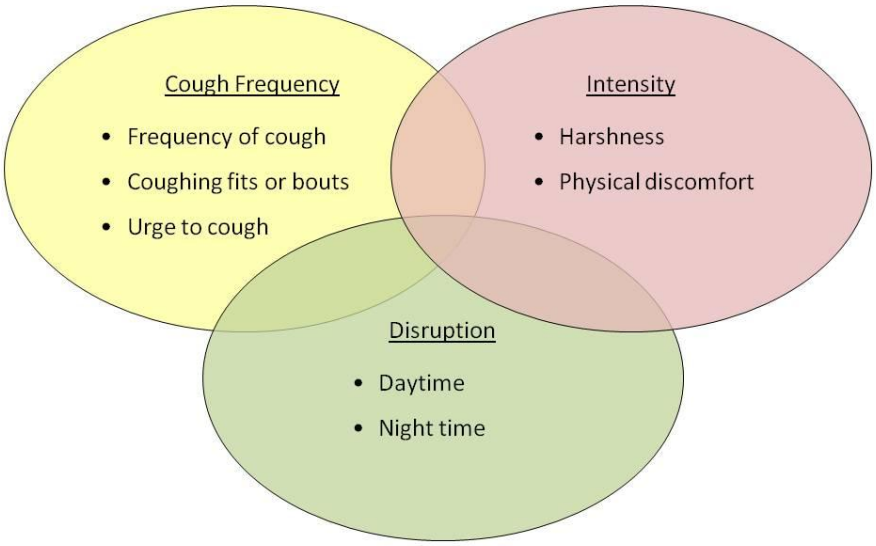
1.3 Subjective assessments of cough

Assessment of treatment efficacy depends on demonstration of a partial or complete response. The way in which this response is measured is therefore of paramount importance since it is the cornerstone by which physicians determine whether to maintain the patient on treatment or change to another trial of therapy. A valid measure of cough could therefore quantify cough severity, determine treatment efficacy and indirectly yield diagnostic information [16].

Currently available subjective and objective tools assess different aspects of cough and its impact on quality of life. No standard measure is universally accepted. Vernon et al recently conducted a qualitative focus group study and identified 3 domains which chronic cough patients perceive as important determinants of overall cough severity: cough frequency, cough intensity and degree of disruption (Figure 1-6) [137]. The authors recommend high precision tools for assessing cough severity, but emphasise that these measures ought to be concordant with the features important to patients. Indeed, it is postulated that a single severe bout of coughing causing incontinence may be of more importance to some patients than the hundreds of barely noticeable coughs [139].

The subjective assessment of cough has been better studied than objective assessments, but recent technological advances have brought about several new tools. The available cough severity measures and their advantages and limitations are reviewed here.

Figure 1-6 Dimensions of cough severity



Adapted from Vernon et al (2009) [140]

1.3.1 Cough symptom scores

Cough symptom scores or diaries utilise self-reported estimations of cough frequency and severity. Most cough symptom scores are simple tools that allow a limited number of possible responses. They have been extensively used in studies on cough but good evidence to support their validity is lacking. The repeatability of cough symptoms scores has not been reported, and the reproducibility of symptom questions relating to cough is questionable. One study demonstrated kappa coefficients ranging only from 0.27 -0.58 [141].

Much of the studies on the accuracy of subjective cough frequency scores have been conducted in paediatric subjects. Hamuctu et al found no relationship between cough symptom score and objective daytime or nighttime cough frequency in children with cystic fibrosis [142]. Chang et al also compared subjective scoring of cough against objective cough frequency, using both parent and child-reported visual analogue scales and Verbal Category Descriptive scores (VCD) [143]. The VCD comprised a 5-point scale rating the frequency of cough. The best relationship was found between the daytime cough frequency and daytime VCD (r=0.63 to 0.65). Nighttime relationships were poor. Falconer et al evaluated

subjective assessment of nocturnal cough in asthmatic children against objective cough recordings [144]. The subjective score was a simple binary assessment (whether nocturnal cough was present or not) but poor agreement was found between subjective and objective measures (Kappa 0.30). Hsu et al reported a statistically significant correlation between cough symptom score and cough frequency, but the magnitude of that correlation was not given [119]. The relationship was only applicable to daytime cough, presumably because subjects are cannot accurately quantify coughs occurring in and around sleep periods.

The poor relationship between cough symptom scores and objective cough frequency may be due to the wording of questions within the scores, which do not always specifically refer to frequency of cough. Non-specific wording may allow other aspects of cough severity to influence scoring.

1.3.2 Cough severity visual analogue scales

Cough visual analogue scales (VAS) are 100 mm linear scales on which patients can demarcate self-perceived cough severity. The scale is anchored at each end by a phrase to denominate extremes of possible cough severity range: for example, *no cough* and *worst cough*.

The cough VAS has been shown to be repeatable in patients with chronic obstructive pulmonary disease, yielding a within-subject standard deviation of 7.75 mm and intra-class correlation coefficient 0.87 [145]. The cough VAS is also highly repeatable and responsive in chronic cough, with an intra-class correlation coefficient 0.84 and an effect size of 3.2 [11]. However, it does not relate well with cough frequency in children (r=0.47 to 0.55) or adults (r=0.38) [143, 146]. This may not be surprising since cough VAS is usually worded to assess subjective perception of global cough severity, and cough frequency is only one component of overall cough severity. It is unknown how well cough VAS relates to objective measures of cough intensity.

In a study of 104 patients with chronic cough, the mean cough VAS was found to be 48 mm [11]. In another study of 62 patients, mean daytime and night-time VAS was

40 mm and 18 mm respectively [147]. Cough VAS has also recently been reported in 30 otherwise healthy subjects with acute viral cough [148]. In this study, the mean cough VAS was 39 mm and the minimal important clinical difference (MICD) was 13 mm [148].

1.3.3 Health status questionnaires

A number of health related quality of life questionnaires have been developed to specifically address cough-related health status. Whilst they assess the impact of cough rather than cough severity *per se*, they have become standard outcome measures in studies investigating chronic cough.

The Leicester Cough Questionnaire (LCQ) comprises 19 items within 3 domains: physical, psychological and social [11]. It has been widely validated in chronic cough, and an adapted version has been validated in acute cough [11, 148, 149]. The LCQ is repeatable and responsive in acute and chronic cough, with a minimal important clinical difference of 2.5 and 1.3 respectively [11, 148, 149]. It has been used as an outcome measure in randomised clinical trials of gabapentin and erythromycin for chronic cough [88, 148]. The LCQ is also validated for use in patients with COPD and has been found to be reproducible in patients with idiopathic pulmonary fibrosis [150, 151]. Its use has also been reported in patients with cystic fibrosis, bronchiectasis and asthma [152-154].

The Cough Specific Quality of Life Questionnaire (CQLQ) comprises 28 items which are divided into 6 domains: physical complaints, psychosocial issues, functional abilities, emotional well-being, extreme physical complaints and personal safety fears [12]. Good construct validity and internal consistency were shown in both acute cough and chronic cough, and repeatability and responsiveness was demonstrated in the chronic cough cohort [12]. The minimal clinical important difference of the CQLQ has not yet been reported. Nevertheless, the CQLQ has been used to assess cough in a number of respiratory disorders including COPD, asthma and bronchiectasis and has been used as an outcome measure in a randomised controlled trial of acid suppression therapy in chronic cough [69, 155].

The Chronic Cough Impact Questionnaire (CCIQ) comprises 21 items divided into 4 domains: sleep/concentration, social relationship, impact on daily life and mood [156]. Its development was derived from 166 patients with chronic cough and the construct validity, internal consistency and repeatability met required standards. Concurrent validity was poor when assessed against the Short Form 36 (SF36) generic health status questionnaire, with only one of the CCIQ domains (impact on daily life) showing a weak correlation with 4 of the SF36 domains (r=-0.008 to 0.367) [156]. The tool was deemed responsive after a significant difference in 16 of the 21 items was recorded following treatment [156]. The effect sizes or minimal important clinical differences were not reported. Scores have only been reported for the individual item and domains scores, and no mean overall composite score was reported in the development studies [156, 157]. The responsiveness of the overall tool is also unknown. At the time of writing, there were no published clinical trials that have used the CCIQ as an outcome measure.

1.4 Objective assessment of cough frequency

Objective cough frequency assessment is recommended by the European Respiratory Society task force as part of the assessment of cough severity to improve clinical practice, research and assess new therapies [79].

The gold standard method in cough frequency monitoring was previously held to be that obtained from video recordings [158]. However, the impracticality of confining subjects to an observation room for several hours prompted the study of digital audio recordings, which could allow ambulatory measurements in the subject's home environment. Coughs produce a characteristic sound that can be counted from playback of sound recordings. Excellent agreement has been demonstrated between cough frequency counted from audio recordings and that from video recordings, with an error of only 0.1 to 0.3 coughs per hour [159]. This has led to the proposition of audio manual cough counting as the new gold standard.

1.4.1 Early methods of objective cough frequency assessment

Early examples of objective cough frequency assessment date back to 1954, when Gravenstein et al recognised the limitations of subjective estimations of cough frequency for assessing the effect of antitussive agents [160]. They described a technique using an instrument developed by Albert Grass of the Grass Instrument Company, which consisted of an inkwriting apparatus that recorded coughs by depicting the cough sounds on moving paper as spikes [160]. The investigators analysed the number of cough spikes (cough frequency), spike duration and amplitude, and the duration of cough bouts in response to tussive challenge tests. The interest in recording sound for the purpose cough monitoring continued and subsequent developments led to use of tape recorders instead of inkwriters [161] [162]. In the 1960's, Woolf et al adopted a system in which a free-field microphone was fixed in place above the head of a bed and connected in series to a tape recorder [161]. The tape recorder was triggered to record if the microphone detected any sound, and would then continue recording for 5 seconds after the end of the sound activity. This trigger-activated recording method allowed 24 hours of monitoring to be captured on a 2-hour tape. The setup necessitated subjects to be

confined to a hospital room which was isolated as much as possible from ambient noise.

Alternative devices to free-field microphones for recording cough sounds were later employed. In the late 1970's and early 1980's, Rühle et al and in Matthys et al used contact microphones attached to the throat [163, 164]. The contact microphones were essentially pressure transducers that were fixed over the larynx which some subjects reported as uncomfortable. The sound signals were relayed to a recorder, which was activated by coughs but not other sounds such as speech, and was capable of 8 hours of monitoring [163, 165]

By the late 1980's, the addition of on-line processing techniques was incorporated into cough monitoring systems in order to filter cough detection from other sounds or manoeuvres. Salmi et al developed a system that comprised of simultaneous sound and body movement detection [166]. Body movements were sensed using a kinesthetic transducer paired with a static charge-sensitive bed mattress whilst subjects were observed lying or sitting on the bed. Coughs were only labelled if pre-set thresholds of noise and movement levels were detected by both the microphone and the movement sensor. They were one of the first investigators to provide validation data of the performance of their cough detection system, against a reference of manually triggered recording of coughs by a trained observer. Performance was good, with a sensitivity and specificity of 99% and 98% respectively, but the major limitations included restriction of the subject to the bed and the need for subjects to refrain from making any high frequency noise or sudden movements.

1.4.2 Modern cough frequency monitoring systems

The ideal objective cough monitoring system requires excellent accuracy of course, but other desirable features are portability and automation - to make the system practical for clinical use and reduce the time-consuming nature of manual cough counting. A number of systems have recently been reported. Most are still based on the detection of the cough sound, which is reasonable since it is our recognition of the characteristic sound that we use to identify cough. Some systems use

accelerometers to measure vibration in place of sound, and others have combined the use of sound with electromyography [167, 168]. Each system has its own advantages and disadvantages and these are described below. In general, whilst cough sounds are simple to record and interpret in a controlled environment, their analysis is challenged by ambient noise when monitoring systems are made ambulatory. Speech, throat clearing, laughter and sneezing are some of the non-cough sounds that can lead to false positives [169]. Complex computer algorithms are often used to differentiate cough sounds from ambient noises in order to facilitate automated analysis. The technical aspects of these detection algorithms are not within the remit of this thesis. The main cough monitoring systems are described below and their validation studies summarised in Table 1-3. At the time of submission of this thesis, only 2 of the cough monitoring systems were available and in use, the Leicester Cough Monitor and VitaloJak.

Leicester Cough Monitor

The Leicester Cough Monitor (LCM) is a sound-based system that allows ambulatory 24-hour monitoring. One key advantage of the LCM system above some of the other cough monitoring systems lies in the automated aspect of the analysis method and minimal user input requirement, allowing a final report to be generated after approximately one hour of analysis [170]. The system works by automated analysis and detection of candidate cough sounds using custom software based on Hidden Markov Models speech recognition algorithms [171]. Following an initial automatic analysis of the recording, a selection of the detected candidate sounds are validated by an operator and the results from the validation process are then incorporated back into the programme in order to refine the detection algorithm (Figure 1-7) [172]. The operator input improves sensitivity and acts as a real-time calibration method to account for individual cough sound differences. The LCM was originally validated in patients with chronic cough and in healthy controls. Initial validation was performed against manual cough counting of 6-hour recordings, with further subset analysis of two single hour-long epochs

extracted from 18-hour recordings [172]. The 6-hour validation study showed that 95% of manually marked coughs were labelled by the programme as candidate cough events, although presumably with significant false positive rates. Following user refinement, overall cough detection sensitivity and specificity were reported as 86% and 99% respectively. Data from the longer recording validation study showed that the user refinement process improved the sensitivity and specificity to 98%, compared with manual analysis of all the pre-user refinement candidate events. The overall performance of the LCM in the longer subset analysis was better than that of the 6-hour group, with a sensitivity 91%, specificity 99% and false positive rate of 2.5 coughs per hour [172, 173]. The agreement between the LCM counted cough rates and manually counted cough rates was 0.87. LCM counts were also repeatable over 6 hours, with an intra-subject SD of 11 coughs/pt/hr and an intra-class correlation coefficient of 0.9. The short duration of these validation studies for a 24-hour cough monitoring system led to some criticism, but later external validation studies performed over a 24 hour period reaffirmed the good correlation (r=0.97) and agreement (r=0.98) between LCM counts and manual cough counts [169, 172, 174]. A further recent 24-hour validation study in patients with chronic cough and healthy controls found the LCM to have a sensitivity and specificity of 82-84% and 99.9% respectively [175]. The LCM has been used as an outcome measure in randomised controlled trials of gabapentin and erythromycin [88, 176].

Figure 1-7 Leicester Cough Monitor set up and analysis

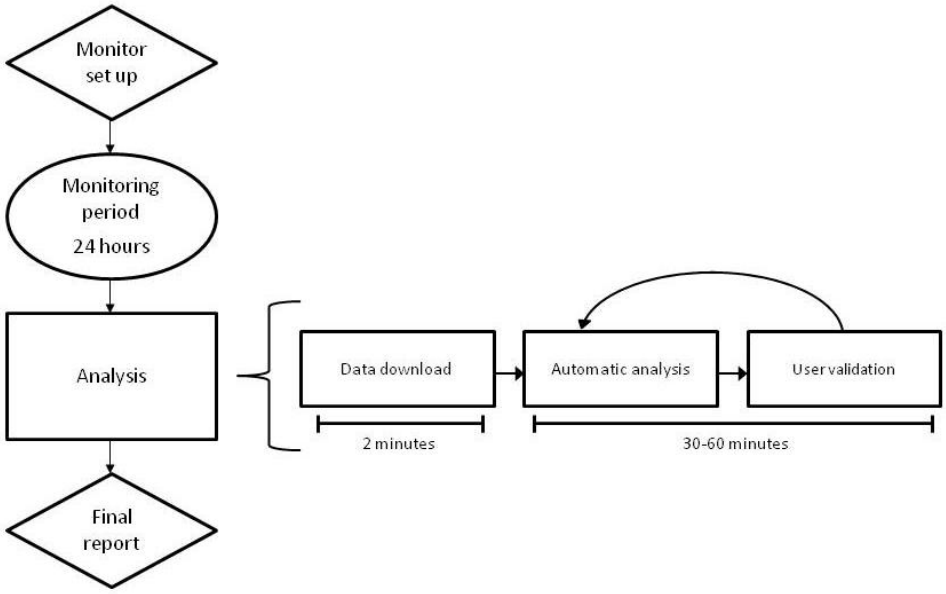


Diagram outlining the Leicester Cough Monitor set up and analysis process.

Vitalojak

The Vitalojak is a custom-built cough recording device paired with a lapel microphone which is capable of ambulatory 24-hour monitoring [177]. The recording, once uploaded onto a computer, is compressed (by removing periods without any sound) and then manually analysed via an audiovisual display. During its evolution, the developers have used different recording devices to capture the data, but the analysis technique is well established. Early validation studies of this technique during overnight monitoring in 8 patients with chronic cough showed excellent agreement with cough counts from video recordings and a mean difference of 0.3 coughs/hr, which was within one standard deviation [178]. The excellent results are not surprising since the Vitalojak uses manual cough counting from audio recordings, which was previously shown to be as good as video recordings [159, 178]. The major limitations of this technique are the laborious manual counting method due to the lack of automation and the need for operator experience and training. Nevertheless, the system has been used as a cough monitoring tool in a number of clinical studies of patients with chronic cough, COPD and pulmonary fibrosis [72, 151, 159].

Hull Automatic Cough Counter

The Hull Automatic Cough Counter (HACC) is another sound based cough monitoring system which operates by compressing the sound recording and then identifies coughs using a neural network algorithm which is trained to recognise specific features based on reference "coughs" and "non-coughs" [179]. 33 subjects were recruited for the original development study, of which 23 were studied for the purpose of defining the reference cough features, leaving 10 subjects for the validation phase [179]. The monitoring period of the validation phase was limited to one hour in duration. At the time of publication, the HACC was not fully automated and required manually verification and counting of the detected coughs. The average sensitivity and specificity of the Hull Automatic Cough Counter for cough detection, using manual audio cough counting as the reference, was 80% and 96%

respectively. There was a 20% false positive rate attributed to ambient sounds that included coughs from sources other than the subject undergoing monitoring. This limitation arose because the recordings for the study took place within a clinic where other coughing patients were present. Faruqi et al used a newer version of the HACC to investigate cough frequency in patients with chronic cough [146]. Cough monitoring was performed over a 24-hour period, and validation of the system was performed against manual cough counts in 10 patients with chronic cough. Although there was good agreement between the HACC version ii and manual cough counts ($r=0.87$), the HACC consistently underestimated cough counts (HACC vs. manual 24-hour cough counts 237 vs. 546 coughs, $p<0.001$). This may be due to the algorithm applied to the recordings, developed to wean out periods without sound and reduce analysis time but perhaps at the expense of losing low intensity cough sounds.

RBC-7

Munyard et al developed the RBC-7 cough monitoring system, a multi-parametric system incorporating sound, electromyography and electrocardiography data in unison [180]. The RBC-7 can record for a continuous period of 6 hours, or intermittently for 48 hours if set to trigger upon EMG activity reaching a set threshold. Recorded coughs were counted manually. The bulk of the study by Munyard et al focussed on the identification of optimal chest wall positions for the EMG surface electrodes, to aid cough detection and differentiate from other manoeuvres such as speech, throat clearing and sneezing. The validation study was performed in daytime recordings from 10 subjects (4 adults and 6 children) and overnight inpatient recordings of 1-8 hours duration from a further 10 children with cystic fibrosis [180]. The reference was an additional separate audio recording, which was analysed manually. Coughs counts identified with the RBC-7 system correlated strongly with manual cough counts ($r=0.99$), with equally good performance for both day and nighttime analyses. The authors admitted limitations of such a system including the need for EMG expertise, cost and lack of automation,

although Hsu et al also used this technology within their Brompton Cough Recording system in a study of cough frequency in healthy subjects, stable asthmatics with cough and patients with chronic cough [119].

Logan Sinclair LR 100

A later modification of the RBC-7 system led to the development of the LR 100 system [142]. In the validation study by Hamutcu et al, the investigators used an algorithm to remove periods within recordings which were void of any sound signals, shortening the analysis time by several hours, but the identification and counting of coughs remained manual [142]. In this study, 14 children with cystic fibrosis underwent simultaneous monitoring with the LR 100 and a separate conventional tape recorder during chest physiotherapy sessions. There was good agreement between the two methods and the mean difference was within two standard deviations (Table 1-3). The LR 100 has also been validated in pre-school infants, with a resulting sensitivity of 81% and positive predictive value of 0.8 [181].

Adapted Holter monitor cough meter

Chang et al also combined cough sound and EMG for cough monitoring with their adaptation of a Holter monitor [167]. A contact microphone was attached to the skin just inferior to the substernal notch and EMG surface electrodes placed at the xiphisternum and both costal margins. The cough meter was capable of continuous monitoring for 24 hours. Data analysis, cough identification and counting were performed manually by visual playback on a display monitor. Validation of the cough meter was performed in a group of children with recurrent cough and healthy children, and compared against a separate sound recording from a static bedside microphone, which was also scored manually. The agreement was good, although the cough meter tended to capture more coughs than the standard tape recorder, possibly due to the limitations of the older stationary system, which would fail to capture cough sound if the child moved away from the bed or the

sound was, muffled (Table 1-3). Although inexpensive, the main disadvantage of the system is the lack of automation, necessitating time-intensive analysis [167]. This system has been used by the same group in further studies comparing modalities of cough assessment in children with recurrent cough [143, 182].

Lifeshirt®

The Lifeshirt® system incorporates respiratory inductance plethysmography together with a contact microphone, an accelerometer and ECG monitoring [158]. The multiparameter system is capable of recording 24 hours of data and can yield information on cardiorespiratory indices, body position and sound profiles. Analysis is performed once the data is uploaded into a central computer, and a software algorithm identifies cough events. Validation of the system was performed for 24 hours of monitoring in 8 patients with COPD under laboratory conditions [158]. Cough counts detected by the Lifeshirt® system were compared with manually counted coughs from video and audio recordings. Although results were promising, there have been no larger scale validation studies in other patient groups and the system has not yet been used in clinical studies. The performance of the system for cough detection is given in Table 1-3.

Other systems

Subburaj et al developed a computerised cough acquisition and analysis system, using cough sound data acquired from a microphone which was then recorded using a digital audio tape [183]. Analysis is performed by playing back 30-minute segments of data and manual labelling of coughs. The system is able to measure cough sound energy, proposed by the authors as a measure of cough effort. Accuracy was reported as 100% although the validation methodology and reference used to assess accuracy are unclear. Furthermore, sample size was limited to eight 30-minute files obtained from one subject. The system was later made portable and used as an outcome measure in six clinical studies assessing the antitussive efficacy

of dextromethorphan in acute cough [184]. All six studies were similar in design, although two studies used an accelerometer to acquire the cough signal instead of a microphone. The meta-analysis by Pavesi et al reported that the consistent findings across the studies confirmed the validity of the system [184]. No comparison was made between the performance of this system and other standard cough counting techniques.

Paul et al developed a portable self-contained system using an accelerometer positioned at the suprasternal notch to measure vibration [185]. Validation was performed in 15 subjects of varied ages against manual counting from video recordings as a reference. The recordings were performed within hospital and at home but for a short duration, ranging from 15 to 60 minutes. Excellent agreement between the two methods was found (Table 1-3). At the time of writing, there were no further studies validating the system over longer periods.

Table 1-3 Studies of cough frequency monitoring systems

	System	Detection parameters	Automatic or manual counting	Reference for validation	Sample size for validation	Validation period	Validation performance
Barry, 2006 [186]	HACC	Sound	Automatic detection with manual counting	Manual analysis by 2 human listeners	10 smokers with chronic cough	1 hour	Sens 80%; spec 96%
Munyard, 1994 [180]	RBC-7	Sound, EMG & ECG	Manual	Manual from separate audio recording	10 subjects for daytime; 10 children with CF for night time	1-8 hours	r=0.99
Hamutcu, 2002 [142]	LR 100 & modified analysis	Sound & EMG	Semi-automated	Manual from separate audio recording	14 children with CF during chest physiotherapy session	n/a	r=0.96
Corrigan, 2003 [181]	LR 100	Sound & EMG	Manual	Manual from audiovisual recordings	9 infants with cough; 17 healthy infants; total of 38 recordings	Up to 18 hours	Sens 81%; spec not reported. PPV 80%
Matos, 2006 [171] Birring, 2008 [173]	LCM	Sound	Semi-automated	Manual	18 chronic cough; 8 healthy subjects	6 hours and two single hour	Sens 86%; spec 99%; ICC 0.87
Yousaf, 2013 [175]	LCM	Sound	Semi-automated	Manual	12 patients (asthma, eosinophilic bronchitis, chronic cough, COPD); 8 healthy subjects	24 hours	Sens 82-84%; spec 99.9%; ICC 0.85-0.98
Faruqi, 2011 [146]	HACC version ii	Sound	Automated	Manual	10 chronic cough	24 hours	Manual vs. HACC 546 vs. 237 c/hr, p<0.001; r=0.87

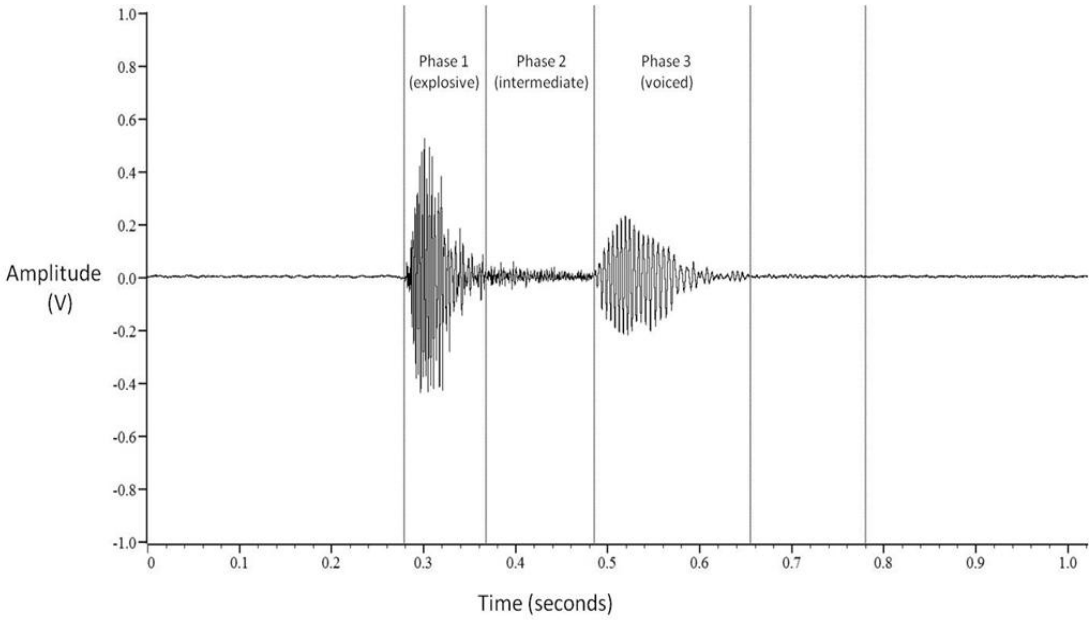
Chang, 1997 [167]	Adapted Holter Monitor	Sound & EMG	Manual	Manual from separate audio recording	15 children with recurrent cough; 3 healthy controls	8.5 hours overnight	Mean difference -0.3 (-0.7 to 0.2) c/hr; limits of agreement -2.2 to 1.7 coughs/hr
Paul, 2006 [168]	Accelerometer (adapted from Subburaj)	Accelerometer	Manual (but shortened analysis)	Manual from video recording	15 subjects with cough (aged between 2 weeks - 84 yrs)	15-60 minutes	ICC 0.93-0.97
Coyle, 2005 [158]	Lifeshirt® system	Sound, ECG, respiratory inductance plethysmography & accelerometer	Automated	Manual from video and audio recordings	8 COPD	24 hours	Sens 78%; spec 99.6%; PPV 84.6%; NPV 99.4%; Accuracy 99%; kappa 81%
Smith, 2006 [178]	Vitalojak	Sound	Manual	Manual from video recording	9 chronic cough	Overnight	Mean difference -0.3 c/hr
Subburaj, 1996 [183]		Sound	Manual	n/a	1 subject	4 hours	Accuracy 100%

HACC: Hull Automatic Cough Counter; LCM: Leicester Cough Monitor; Sens: sensitivity; Spec: specificity; EMG: electromyography; CF: cystic fibrosis; PPV: positive predictive value; ICC: intra-class correlation coefficient; c/hr: coughs per hour; NPV: negative predictive value; Acc: accuracy.

1.4.3 Cough sounds

In the classic form, cough produces a double sound, as shown in Figure 1-8. This sound signal can be divided into three component phases: the explosive, the intermediate and the voiced phases (or phases 1, 2 and 3 respectively), and the first and last phases are responsible for the typical double sound. Whilst all coughs contain the first phase, only some contain a voiced phase [187, 188]. Reports suggest that the voiced phase may be absent in approximately one third of coughs from healthy subjects and possibly more frequently in disease states [115, 187, 189]. There is, however, no relationship between the number of cough sound components and aetiology of cough [190].

Figure 1-8 Cough sound signal

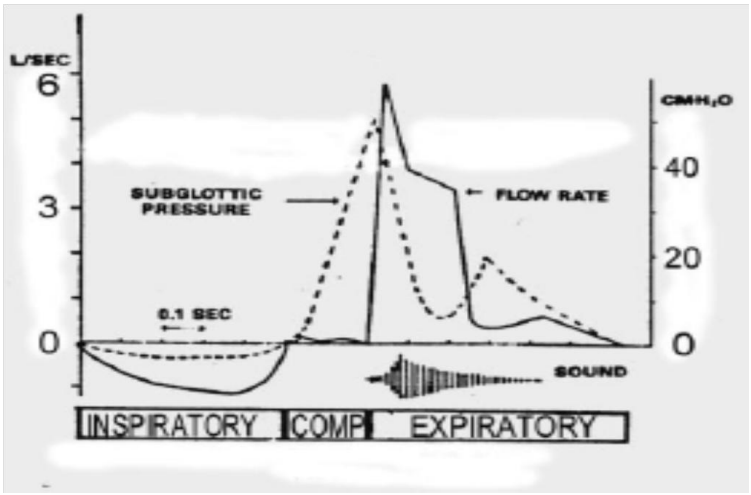


Sound signal of a cough showing 2 peaks in sound amplitude corresponding to the characteristic double cough sound. Trace is of a voluntary cough in a female patient with chronic cough.

The generation of cough sound is dependent on laryngeal and nasopharyngeal structures and airflow from the thorax [191]. It is unknown how much each of those contributes to the nature of the sound. In normal cough, the glottis is fully open

during the inspiratory phase and closes transiently during the compression phase whilst an expiratory effort ensues, allowing sub-glottic pressure to rise. The glottis then opens for the explosive phase of the cough manoeuvre and the turbulent flow of air produces the first characteristic cough sound (Figure 1-9). The quieter intermediate cough sound phase relates to steady state flow through the open glottis, and the voiced phase occurs secondary to glottis narrowing at the end of the expulsive phase [115].

Figure 1-9 Temporal relationship between sub-glottic pressure, flow and cough sound generation



Reproduced from McCool (2006) [109]

Although variation is noted, some characteristics of the cough sound have been described. The duration of the cough sound in normal subjects is approximately 410 ms, although in asthma and chronic bronchitis the duration may be as long as to 600 ms [192, 193]. Murata et al reported a shorter mean cough sound duration, less than 355 ms for healthy subjects or patients with chronic bronchitis [188]. Piirila et al reported ranges for the frequency spectrum profile of cough sounds [194]. They reported a fundamental frequency (also known as maximum frequency) of 436 Hz ± 544 Hz across a range of respiratory conditions and the lowest upper frequency limit of 5,400 Hz, in asthmatics. Korpas et al found the upper frequency limit to be at 3,000 Hz [195].

A host of cough sound parameters have been assessed with varying aims including the distinction between cough and speech, detection of abnormal lung function or as a proposed measure of cough effort [184, 187, 196]. Smith et al investigated the ability of healthcare professionals to identify respiratory disease aetiology by listening to cough sounds [197]. The observers were able to differentiate wet from dry cough but they were unable to discriminate between idiopathic pulmonary fibrosis, asthma, COPD, bronchiectasis or laryngitis [197].

Cough sound detection and analysis forms the basis for most cough frequency monitoring systems. These are discussed in more detail in section 1.4.2. Few studies however, have validated cough sound as a measure of cough intensity or strength.

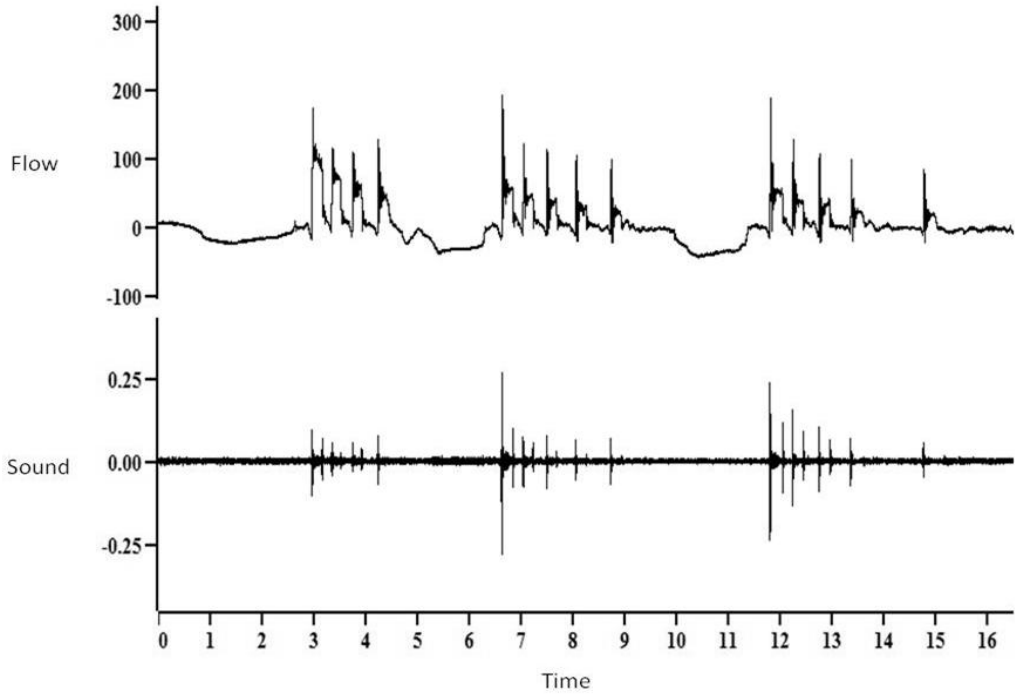
1.4.4 Relationship between cough frequency and subjective cough severity

Cough frequency may be an outcome measure in its own right, but its importance to overall subjective cough severity can be implied by their relationship. A number of studies have confirmed, at best, a moderate relationship between objective 24-hour cough frequency and subjective cough-specific quality of life, with reported correlation coefficients ranging from 0.36 to 0.71 [120, 147, 153, 159, 198]. The modest relationship highlights that the number of coughs is not the only factor important to patients' perception of cough severity. Intensity of cough and the degree of disruption caused by cough are also important [137].

Coughs can occur in isolation or within bouts or peals (Figure 1-10). Cough counts differ depending on whether the individual events within a cough bout are considered separate. Kelsall and colleagues investigated the importance and relevance of these methodological differences by comparing the relationship between the different methods of counting cough and subjective cough severity and cough-related quality of life [120]. They examined three methods of counting coughs - cough explosive phases (number of individual characteristic cough sounds), cough seconds (number of seconds containing at least one cough) and cough epochs (number of periods of continued coughing separated by at least 2 seconds) - and compared these with cough severity VAS and LCQ score. Cough explosive

phases and cough seconds were in good agreement with each other and correlated equally well with VAS and LCQ, but cough epochs performed less well [120].

Figure 1-10 Airflow and sound waveforms for a bout of coughs



14 explosive phases are organised within 3 cough bouts. Upper trace is flow rate and lower trace is cough sound signal. Trace obtained during capsaicin challenge testing in a male patient with chronic cough.

1.4.5 Cough frequency in health and disease

Estimates for expected cough frequency in health and disease can be deduced from many of the cough monitoring validation studies listed in Table 1-3.

In healthy subjects, cough frequency rates of 2 ± 1 coughs per hour are reported, although this study was limited to 6-hour monitoring periods in only eight male subjects [173]. A more recent study in a larger cohort of 44 male and female healthy subjects, using the same technology, demonstrated 24-hour total cough counts of 18.6 coughs (equivalent to cough frequency of 0.8 coughs per hour) [175]. Sumner et al also demonstrated similar findings in healthy non-smokers (median cough

frequency 0.7 coughs per hour), although smokers had higher cough frequency, 5.3 coughs per hour [199].

Objective cough frequency rates in patients with chronic cough have been well documented in several studies, with reported 24-hour cough frequency rates ranging from 16 to 33 coughs per hour [119, 120, 173, 175]. Cough frequency has also been reported for a number of other conditions. In a group of 8 patients with COPD undergoing video monitoring, the mean cough frequency was 33 coughs per hour [158]. The median 24-hour cough frequency in asthmatic patients was found to be 11.8 coughs per hour [119]. Two studies have described cough frequency in patients with cystic fibrosis during inpatient admissions for pulmonary exacerbations, with one study including 14 children and the other including 19 adults [142, 200]. Cough frequency in the paediatric study was counted in cough epochs or bouts and not as individual events; cough frequency rates were unchanged between admission and at discharge (baseline daytime cough frequency 18.2 ± 8.4 cough epochs per hour and night-time cough frequency 5.8 ± 2.9 cough epochs per hour) [142]. The adult study reported cough frequency as time spent coughing, and did demonstrate a fall in both daytime and night-time cough frequency between admission and discharge (median (IQR) admission vs. discharge daytime cough frequency 21.2 (14.0-34.9) vs. 9.0 (5.8-12.8) cough seconds per hour and night-time cough frequency 4.8 (1.0-6.8) vs. 1.5 (0.8-5.0) cough seconds per hour) [200]. The same investigators also investigated cough frequency in idiopathic pulmonary fibrosis, showing overall 24-hour cough frequency rates of 9.4 coughs per hour, although the range was wide (1.5 to 39.4 coughs per hour) [151].

In contrast to chronic cough, there is relatively little data for cough frequency in acute cough. Two community-based studies reported on the duration of acute cough and other related symptoms, but the assessments of cough were subjective and, furthermore, up to 50% of subjects in those studies had used antitussive treatments [201, 202]. In the meta-analysis of dextromethorphan efficacy in acute cough by Pavesi et al, objective cough frequency was measured [184]. Similarly, Lee et al used objective measures to examine the placebo effect on cough frequency [203]. In both studies however, cough monitoring periods were short (between 15

minutes and 3 hours). The former study included a placebo group, which is susceptible to significant placebo effect, as established by the latter study. The latter study included a no-treatment group, but the extremely short nature of the observation period (15 minutes) restricts its use for characterising the natural changes in cough frequency in acute cough.

Sunger et al recently reported objective cough frequency in an observational study of acute cough in 54 otherwise healthy subjects [204]. Over-the-counter cough treatments were not permitted, and so the study yielded valuable information on cough frequency rates and repeatability of cough frequency. 24-hour cough frequency was measured on two consecutive days. Geometric mean cough frequency was 12.1 coughs per hour at baseline and reduced significantly to 2.9 coughs per hour on the following day. The minimal important clinical difference in cough frequency was not assessed. The study period was 2 days in duration and the median duration of cough at baseline was 4 days, but other studies have shown that half of subjects with acute cough report ongoing symptoms 10 days after onset [201, 202, 204]. There is no objective cough frequency data for this longer period.

1.5 Objective assessment of cough intensity

Most studies involving measures of the intensity of coughs have been conducted in the context of assessing cough as a function (Table 1-4). This is most relevant in cases where the efficiency of cough as a defence mechanism is in question, that is, in possible cases of weak cough. This includes neuromuscular diseases, stroke, Parkinson's disease and laryngectomised patients [4, 205-207]. Therefore, the measure by which cough intensity is defined in these studies has generally been with relevance to the ability of cough to perform its underlying physiological purpose – to protect the lungs from aspiration of foreign bodies and clear secretions and debris from the airways. Some of these studies were conducted in healthy subjects but there are few studies assessing cough intensity in patients with chronic cough.

There is no widely accepted gold standard measure of cough intensity [123]. As previously described, the physiological sequence of the efferent cough pathway begins with neurological signalling from the cerebral cortex and cough centre down to the muscles responsible for generating force to elevate intra-abdominal pressure, which is then transmitted to intra-thoracic pressure and leads to rapid respiratory airflow as an output. Based on this sequence, a number of potential methods are available for measuring cough function, including electromyography, cough airflow rates, pressure and sound (Figure 1-11). These are reviewed in detail in the subsequent chapters.

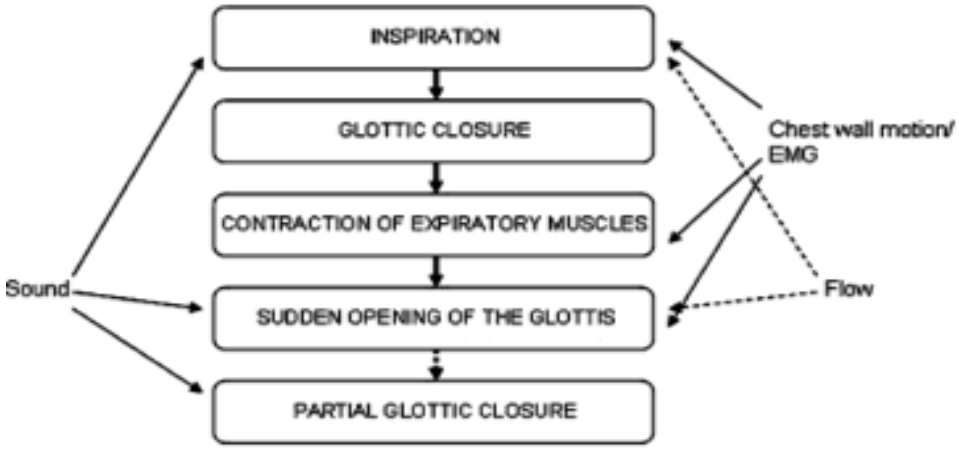
Few studies have examined the intensity of spontaneous cough, presumably due to its unpredictable nature and timing. This has led to the use of experimental models such as voluntary or induced cough using tussive stimuli such as capsaicin. The availability of experimentally induced cough permits evaluation of the efficacy of antitussive agents on cough reflex sensitivity [208]. As shown in studies with codeine however, demonstration of antitussive effect in experimentally induced cough does not necessarily translate into efficacy in pathological cough [209, 210]. This highlights the limitations of using experimental cough to replicate spontaneous cough.

Table 1-4 Selected studies assessing cough intensity or function

Author	Population	Sample size	Cough type studied
Cox, 1984 [211]	Healthy	10	VC/RC
Chaudri, 2002 [1]	Motor neurone disease	53	VC
Chellini 2011 [212]	Laryngectomy	10	VC
Davenport, 2007 [213]	Healthy	NR	RC
Ebihara, 2003 [4]	Parkinson's disease/Healthy	15/15	VC
Fontana, 1997 [214]	Healthy	30	VC/RC
Fontana, 1999 [206]	Laryngectomy/Healthy	10/10	VC/RC
Fontana, 1999 [215]	Healthy	30	RC
Kim, 2009 [216]	Elderly healthy	18	RC
Kyroussis, 1997 [217]	Healthy	6	VC
Lasserson, 2006 [133]	Healthy	10	VC/RC
Lavietes, 1998 [218]	Healthy	5	VC/RC
Lavorini, 2007 [219]	Healthy	19	VC/RC
Lavorini, 2007 [220]	CCHS/healthy children	7/7	VC/RC
Man, 2005 [221]	COPD/Healthy	43/25	VC
Murty, 1991 [222]	Laryngectomy/healthy	10/10	VC
Pitts, 2008 [223]	Parkinson's disease	20	VC
Pitts, 2009 [224]	Parkinson's disease	10	VC
Polkey, 1998 [111]	Amyotrophic lateral sclerosis	16	VC
Reilly, 2012 [225]	Cystic fibrosis/Healthy	10/10	VC
Smith, 2012 [125]	Healthy	16	VC/RC
Smith Hammond, 2001 [2]	Stroke/Healthy	43/18	VC
Steier, 2007 [226]	Suspected respiratory muscle weakness	>500	VC
Ward, 2010 [205]	Stroke/Healthy	18/20	VC/RC

VC: voluntary cough; RC: reflex cough.

Figure 1-11 Opportunities for measurement of cough function



Reproduced from Smith & Woodcock (2008) [227]

1.5.1 Electromyography of the abdominal muscles

Electromyography (EMG) is a method of recording electrical activity from the muscles. The electrical signals arise from action potentials as they propagate along the muscle fibre. The level of EMG activity can therefore be used as a measure of the recruitment of motor units within the muscle of interest. The rate of rise of integrated EMG activity is representative of the rate of recruitment of motor units, while the peak of the integrated EMG activity reflects the total number of units recruited and of their maximum firing frequency [228].

EMG activity can be recorded using needle or fine wire electrodes inserted directly into the muscle [129]. Alternatively, EMG activity can be recorded non-invasively using surface electrodes placed onto the skin overlying the muscle [128, 133]. Surface EMG is easily applied but the signal quality and total activity level can vary with individual differences in body habitus due to interference with signals from skin resistance and subcutaneous fat. The filtering effect from the skin can be improved by preparing the skin to remove dead skin cells and natural oils [229]. Surface EMG is less precise than needle or fine wire EMG, but larger surface area covered by the electrode also means that it can capture signals from a greater number of muscle units and can therefore provide a better indication of muscle function.

A limitation of EMG measurements is the inability to compare values between subjects and indeed between experimental sessions. This is because of the numerous variable factors that can affect the EMG signals including skin resistance, electrode position, distance between electrodes and contact between the electrode and the skin [230]. Raw EMG values can only therefore be compared within subjects and within the same experimental session. Data processing can allow relative comparisons between subjects if the error is eliminated. Normalisation is a method by which values are expressed as a fraction or percentage of another value, often the maximum value observed, and permits comparisons of EMG measurements between subjects [133, 214]. Since both the numerator and denominator (observed value and maximum observed value) for each subject study are measured during the same experimental session and with identical recording settings, any error from the aforementioned factors will affect both values and are hence nullified. Normalised results are expressed in relative units.

EMG of the expiratory muscles has previously been used to quantify cough intensity as early as 1984 and correlates well with cough flow rate [3, 206, 211, 214]. The pattern of motor activation in voluntary and reflex cough has been reported [133]. Abdominal muscle EMG activity has been shown to be repeatable during induced cough challenges performed 30 minutes apart [214].

1.5.2 Gastric pressure

Gastric pressure (P_{ga}) is a reflection of intra-abdominal pressure and can be measured during cough to assess expiratory muscle function [231]. In healthy subjects, cough P_{ga} can exceed 300 cmH_2O during maximal voluntary cough [207]. Reference ranges for cough P_{ga} have been described: 214 ± 42 cmH_2O for males and 165 ± 35 cmH_2O for females [207].

Cough P_{ga} has been advocated as a measure of expiratory muscle strength since coughing is a more natural manoeuvre than that used to measure maximal static expiratory mouth pressure ($P_{E,max}$) and therefore may be an easier technique for patients [207]. There is a linear relationship between cough P_{ga} and $P_{E,max}$ but there is a difference in their ability to identify subjects with respiratory muscle weakness:

Man et al found that 42% of subjects with low $P_{E,max}$ had normal cough P_{ga} whereas only 6% of subjects with low P_{ga} had normal $P_{E,max}$ [207]. In another similar study, both $P_{E,max}$ and cough P_{ga} in isolation were subject to false positives but the use of both tests together resulted in a reduction in the number of cases labelled with weakness from 38% to 27% [232]. The addition of non-volitional respiratory muscle testing using gastric pressure in response to lower thoracic nerve root magnetic stimulation resulted in further reduction in subjects labelled with weakness to 17% [232]. Man et al suggest that these differences may be due to technical limitations related to the manoeuvres including understanding, cooperation and motivation but they also recognise that different manoeuvres do not recruit exactly the same muscle groups [207].

It is important to note that the above studies were of expiratory muscle function, and not specifically cough function. Furthermore, these studies were conducted in patients with suspected expiratory muscle weakness and in healthy subjects. At the time of writing this thesis, no studies have quantified cough P_{ga} in patients with chronic excessive cough or assessed the relationship between cough P_{ga} and subjective cough intensity as perceived by patients.

A major limitation of gastric pressure measurement is the invasive nature, since it requires a balloon catheter to be inserted intra-nasally. This can be done readily in the laboratory, but is associated with some practical inconvenience. The existence of tools such as ambulatory oesophageal manometry supports the feasibility for longitudinal studies using gastric catheters to measure spontaneous cough since both techniques are similar. However, a number of factors may affect baseline P_{ga}, including body position, state of rest of the abdominal muscles or external compression from tight-fitting belts, which may be difficult to account for during ambulatory studies [233, 234].

1.5.3 Oesophageal pressure

Oesophageal pressure (P_{oes}) is a gauge of intra-thoracic pressure and can be measured using a balloon catheter within the oesophagus [235]. Peak P_{oes} during cough is considered to be an important driving force for cough flow but the

relationship between the measures can be variable and both are recommended for physiological studies of cough [236].

P_{oes} increases during the compression and expulsion phases of cough and can reach pressures as high as 250-300 mmHg in healthy subjects [109, 237]. It is not known what pressures can be reached in patients with chronic cough and the importance of cough P_{oes} to subjective perception of cough intensity has not been studied.

Oesophageal manometer devices are available and in clinical use. Similar to gastric pressure measurement, a limitation is the invasive nature since it requires a catheter to be sited within the oesophagus. Another potential disadvantage is that the presence of the oesophageal catheter itself can have an inhibitory effect of cough frequency, and it is therefore possible that cough intensity is also attenuated [238]. Indeed, subjects report lower daytime cough severity VAS when an oesophageal catheter is in-situ [238]. Body position and other actions such as swallowing are also known to influence oesophageal pressure measurement [125, 239].

1.5.4 Cough flow

Many studies have used flow rate as a measure of cough (Table 1-4). Like gastric and oesophageal pressure however, most of these studies assessed cough flow in relation to efficacy of cough as a defence mechanism.

Cough flow rate is easily measured using a pneumotachograph and is non-invasive. In healthy subjects, the maximal voluntary cough flow rates in healthy subjects reported in the literature varies between 276 to 497 L/min, although some have reported upper limits over 800 L/min [125, 205, 214]. Cough flow rates during induced cough can be more challenging to measure due to technical limitations, but Ward et al demonstrated a mean peak cough flow rate of 379 L/min in response to tartaric acid [125, 214].

Cough flow rates are subject to interference from laryngeal activity, since partial or complete closure of the glottis can result in interruption of airflow. Glottis function is integral to the cough manoeuvre, but cough is still possible even without a

functional larynx [222, 240]. Fontana et al found no difference in maximal voluntary cough flow rates between laryngectomised patients and healthy controls, similar to a previous study, although both study sample sizes were small (n=10 for each group) [206, 222]. Time to cough peak flow was longer in laryngectomised patients due to the absence of the compression phase, which is dependent on glottis closure [206]. Chellini et al also reported the absence of compression phase in patients undergoing partial laryngectomy but they found that cough flow was reduced compared to controls [212].

In a recent study by Smith et al, measures of cough flow, oesophageal pressure and gastric pressure were measured during voluntary and induced cough in healthy subjects [125]. They found that the lung capacity prior to coughing (operating volume) affected cough flow rates but not oesophageal or gastric pressures. They were unable to assess cough flow rates during induced cough due to methodological difficulties and since the study was limited to healthy subjects, they did not assess spontaneous cough.

1.5.5 The optimal physiological measure of cough intensity

The optimal physiological measure of cough intensity is not known. There is no recommended gold standard measure or accepted definition of cough intensity. The currently available measures have been described but which of the measures is best remains uncertain. As Fontana states, “you pays your money and you takes your choice” [123]. It seems reasonable that, by virtue of being the furthest downstream, cough flow may be the ideal measure of cough function, but its use as a measure of intensity of cough is seen by some as a disadvantage because flow is a secondary index of cough [123]. Lavietes et al recommended that physiological studies of cough use both measures of flow and oesophageal pressure [218]. It is suggested that objective measure used to assess cough intensity should be relevant to patients’ perception of intensity, but it is currently not known which measure of cough intensity relates best to the patients' perspective [137].

1.5.6 Cough sound: a potential measure of cough intensity

Use of cough sound analysis in clinical practice has most commonly been used for the purposes of cough detection in cough counting monitors. Some investigators have explored the potential for using cough sound to identify cough aetiology or differentiate between productive and non-productive cough [191].

The use of cough sound as a measure of cough intensity has been suggested [184]. Pavesi et al conducted a meta-analysis of 6 studies evaluating the efficacy of the anti-tussive dextromethorphan in acute cough due to upper respiratory tract infection using identical cough sound recording technology and protocols [183, 184]. The outcome measures were derived from the cough sound analysis and included cough counts, cough effort (cough sound power spectral area), and cough intensity (average cough effort per cough). They did not validate their sound parameter against other measures of cough intensity however, so whilst their parameter can be accepted as a measure of *intensity of cough sound*, there is no data to support it as a measure of subjective or objective physiological cough intensity.

Thorpe et al analysed cough sounds from 12 asthmatic and 5 non-asthmatic subjects [187]. Cough flow dynamics were also assessed and the authors assessed the relationship between cough sound and flow. They reported a correlation between sound power and peak cough flow (r=0.42) and between sound duration and average cough flow (r=0.38) for the first phase of cough sound. Additionally, they found an association between standard deviation of distribution of sound energy and peak cough flow for the intermediate phase (r=0.46). The weak relationships may due to the analysis method, which combined coughs from a heterogeneous group of asthmatic and healthy children of mixed ages. It is not known how this could influence cough sounds. Furthermore, only 117 coughs were analysed and the coughs were recorded before and after exercise, which could have altered flow dynamics and hence the relationship between flow and sound.

Goldsmith et al devised a unique system that allowed simultaneous measurement of cough sound and cough airflow [241]. Using this technology, Abaza et al applied

complex principle component analysis on several sound parameters for an algorithm to detect abnormal lung function [196]. The investigators examined over 100 candidate sound parameters including total energy, total power, peak power and dominant frequency (maximum frequency) and they achieved a sensitivity and specificity of 98% for detecting abnormal lung function, but they did not specify which parameters were found to be most important [196]. They also did not assess the algorithm's ability to predict airflow rate quantitatively.

1.6 Unanswered questions on objective measures of cough

1.6.1 Cough frequency

The standard duration for cough frequency monitoring is over a 24-hour period [79]. 24-hour monitoring may be inconvenient for patients however, and can be time-consuming to analyse [146]. The validity of shorter periods of cough monitoring has not been studied, particularly with respect to responsiveness of such a measure. Most coughs occur during the daytime, giving the potential for using shorter daytime cough counts as a surrogate measure for 24-hour cough frequency or as an outcome measure in its own right [119, 173].

Cough frequency in healthy subjects and in chronic cough is well documented, but cough frequency in acute cough is not well described, with few studies having used objective measures. This lack of a consistent and well defined outcome measure is considered partly responsible for the variable efficacy results of antitussive medications in acute cough [25]. The study by Sunger et al provides important objective data on cough frequency rates in acute cough but one of its limitations is its short duration [204]. It is not known how quickly acute cough resolves over a longer period. Furthermore, the minimal important clinical differences in cough frequency remain unknown. Understanding of the pattern of natural recovery in acute cough would allow definition of clinically important differences in cough frequency and inform sample size calculations to power future antitussive efficacy trials [26].

1.6.2 Cough intensity

Objective physiological methods for the measurement of cough intensity are available but the focus in the majority of studies has been on the efficacy of cough function in patients with potentially weak cough or in healthy subjects. Few studies have assessed cough intensity in patients with excessive or chronic cough. Furthermore, much of the current literature on cough intensity originates from the study of voluntary or induced cough and, there is far less data on the study of spontaneous cough. Differences in cough intensity may exist between experimental and spontaneous cough, particularly in patients with pathological cough. A better understanding of these potential differences in cough intensity may help clarify if experimentally induced cough is an appropriate model for testing antitussive agents.

The expiratory reflex sound is similar to the cough sound but physiological differences between the reflexes are recognised, yet most cough studies have not defined which reflex was assessed [107]. It is unknown if measures of cough intensity are different between cough and ER.

Objective measures of cough intensity may be useful to guide clinical practice and assess antitussive drugs in clinical trials. The current methods for the assessment of cough intensity have limitations including their invasive nature or impracticality for ambulatory monitoring. Cough sound analysis has been proposed as a potential method for assessing cough intensity non-invasively but few studies have validated sound against physiological measures of cough intensity.

2 Aims and hypotheses

The aims of this thesis are to develop and evaluate objective measures of cough:

Cough frequency

1. to evaluate cough frequency as an objective outcome measure of acute cough and determine the minimal important difference;
2. to assess the validity of short duration cough frequency monitoring.

Cough intensity

3. to compare physiological cough intensity during voluntary, reflex and spontaneous cough in patients with chronic cough and explore the relationship between physiological and subjective measures of cough intensity;
4. to determine the relationship between cough sound and measures of cough intensity.

My hypotheses are:

1. objective 24-hour cough frequency measurement in acute cough is feasible and the minimal important difference can be quantified;
2. short duration daytime cough frequency accurately reflects 24-hour cough frequency and is a responsive measure in chronic cough;
3. cough intensity differs between patients with chronic cough and healthy controls and between voluntary, induced and spontaneous cough;
4. cough sound measures correlate with physiological measures of cough intensity in health and disease.

3 Materials and methods

3.1 Ethical approval

The studies reported within this thesis were approved by The East London and The City Research Ethics Committee 1, London (REC reference number: 10/H0703/6). All subjects gave their informed written consent to participate.

3.2 Subjects

Patients with chronic cough were recruited from specialist cough clinics at King's College Hospital, London. Healthy volunteers involved in the studies were recruited from staff and students at King's College Hospital and King's College London. Subjects with acute cough were recruited from healthy staff and students at King's College Hospital and King's College London, and from The Corner Surgery General Practice, London.

3.3 Pulmonary function tests

Standard spirometry was measured in all subjects in accordance with international guidelines [242, 243]. Measurements were performed using true volume displacement (Spiro Air®, Medisoft, Sironnes, Belgium), calibrated daily using a 3L syringe (Hans Rudolph Inc, Kansas City, USA). Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured with subjects in the seated position and wearing a nose-clip [242]. Subjects were asked to breathe in as deeply as possible (to maximal inspiration), place their lips around the mouthpiece while ensuring an airtight seal, and then to exhale rapidly with maximal force. A minimum of three technically acceptable efforts were performed until results returned within a 5% error of each other, and the largest value was taken for each given measure. Reference values for predicted FEV_1 and FVC were derived from the European Community for Steel and Coal published data [244].

3.4 Assessment of subjective cough severity

3.4.1 Cough specific quality of life

Cough specific health status was assessed using the Leicester Cough Questionnaire (LCQ) [11]. The LCQ is a 19-item self-completed quality of life questionnaire that was developed for patients with chronic cough (**Error! Reference source not ound.**). The questionnaire uses a 7-point Likert response scale per item and groups the component questions into 3 domains: physical, psychological and social. Each LCQ domain score ranges from 1 to 7, and the overall LCQ score ranges from 3 to 21, with a higher score reflecting better health status [11].

3.4.2 Subjective cough severity

A 100 mm visual analogue scale was used to assess subjective daytime, nighttime and overall cough severity (Figure 3-2). The phrases “no cough” and “worst cough ever” were labelled at opposite ends of the scale to provide anchors by which subjects could rate the severity of their cough.

3.4.3 Change in cough severity

Temporal changes in cough severity were assessed using a Global Rate of Change Questionnaire (GRCQ) which was completed at follow up visits [245]. The GRCQ comprises of a 15-point Likert response scale ranging from -7 to 7 and can be used to establish minimal important differences in outcome measures. (Figure 3-3).

Figure 3-1 Leicester Cough Questionnaire

LEICESTER COUGH QUESTIONNAIRE

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the number of the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1. Every time
2. Most times
3. Several times
4. Some times
5. Occasionally
6. Rarely
7. Never

3. In the last 2 weeks, have you been tired because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

6. In the last 2 weeks, my cough has made me feel anxious

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough:

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

10. In the last 2 weeks, has your cough disturbed your sleep?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

11. In the last 2 weeks how many times a day have you had coughing bouts?

1. All the time (continuously)
2. Most times of during the day
3. Several times during the day
4. Some times during the day
5. Occasionally through the day
6. Rarely
7. None

12. In the last 2 weeks, my cough has made me feel frustrated

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last 2 weeks, my cough has made me feel fed up

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

15. In the last 2 weeks, have you had a lot of energy?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1. Every time
2. Most times
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1. Every time I cough
2. Most times when I cough
3. Several times when I cough
4. Some times when I cough
5. Occasionally when I cough
6. Rarely
7. Never

Figure 3-2 Example of visual analogue scale

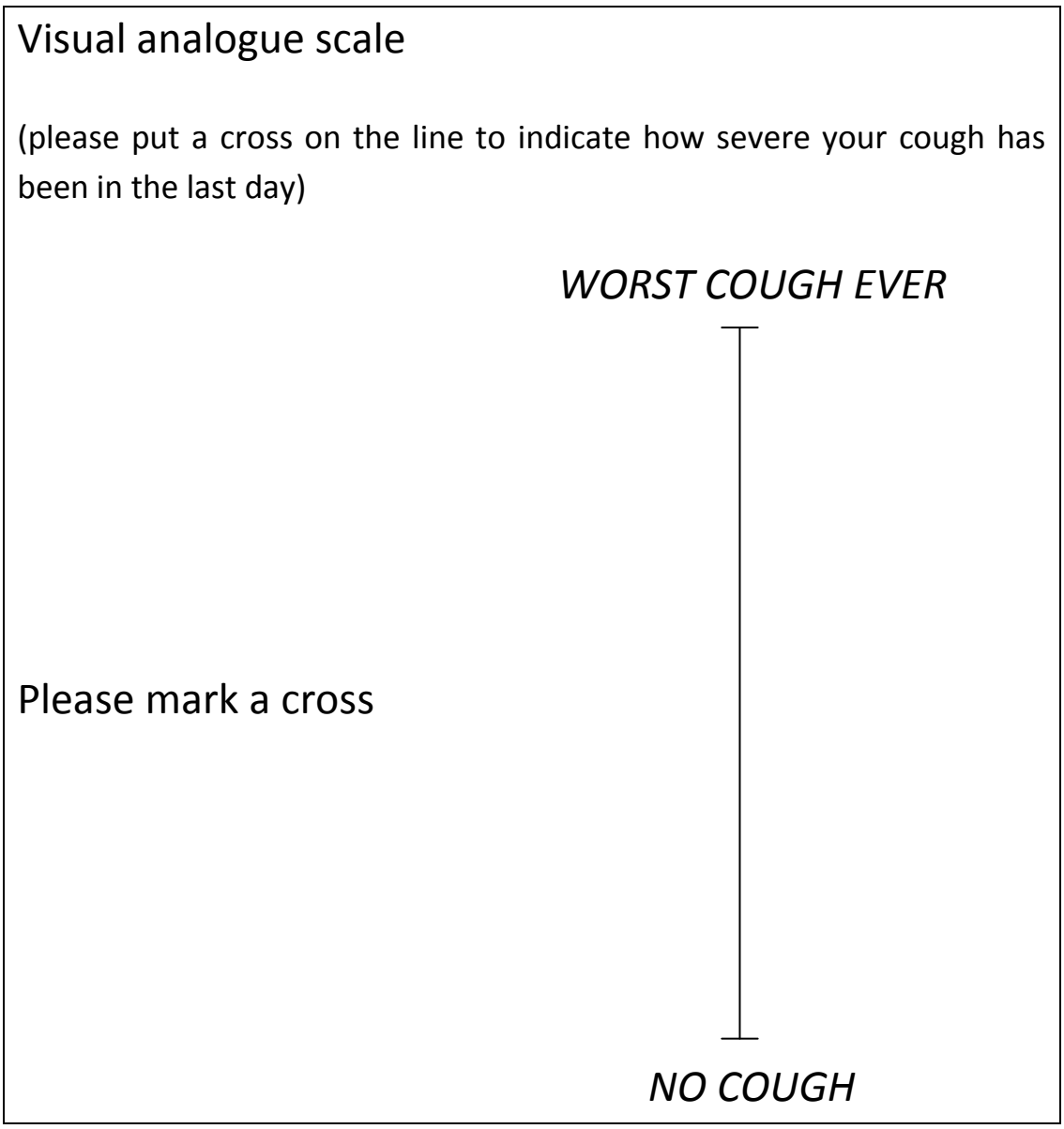


Figure 3-3 Global Rate of Change Questionnaire

Q1. Since your first cough questionnaire, has there been any change in the severity of your cough?

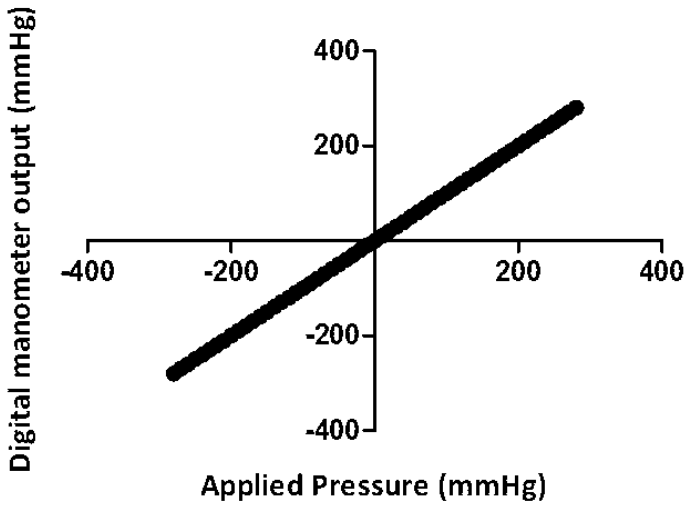
-7	A very great deal worse
-6	A great deal worse
-5	A good deal worse
-4	Moderately worse
-3	Somewhat worse
-2	A little worse
-1	Almost the same, hardly any worse at all
0	No change
1	Almost the same, hardly any better
2	A little better
3	Somewhat better
4	Moderately better
5	A good deal better
6	A great deal better
7	A very great deal better

3.5 Measurement of pressures

3.5.1 Measurement of mouth pressure

Mouth pressure (P_{mo}) was measured relative to atmospheric pressure using a flanged mouthpiece (Hans Rudolph Inc, Kansas City, USA) attached to a manually operated shutter valve. Mouth pressure was measured using a differential pressure transducer (MP45, Validyne, Northridge, CA, USA) attached to the valve via a fine bore catheter. The pressure signal was amplified before acquisition (CD280, Validyne, Northridge, CA, USA). The shutter valve contained an exit port of 2 mm internal diameter, located proximally to the valve. This port introduced a small air leak, thereby preventing glottic closure and reducing the contribution of the buccal muscles during maximum expiratory manoeuvres [231]. 2-point calibration of the mouth pressure transducer system was performed daily against a known applied pressure determined by a digital manometer (C9953, Comark Ltd®, Hertfordshire, UK). The accuracy of the digital manometer was validated against a mercury manometer over the range 0-300 mmHg in a laboratory experiment (Figure 3-4).

Figure 3-4 The linearity and accuracy of the digital manometer



Laboratory experiment showing accuracy and linear relationship between applied pressure as measured by a mercury manometer and observed pressure as measured by the digital manometer.

3.5.2 Measurement of oesophageal and gastric pressure

Oesophageal pressure (P_{oes}) and gastric pressure (P_{ga}) was measured separately using two closed-ended catheters, each 86 cm in length and with a 9.5 cm flexible polytetrafluoroethylene balloon at one end (Cooper Surgical, Berlin, Germany). The balloon catheters were each attached to differential pressure transducers (MP45, Validyne, Northridge, CA, USA). The pressure signals were amplified before acquisition (CD280, Validyne, Northridge, CA, USA). 2-point calibration of the oesophageal and gastric pressure transducer system was performed daily against a known applied pressure determined by the digital manometer.

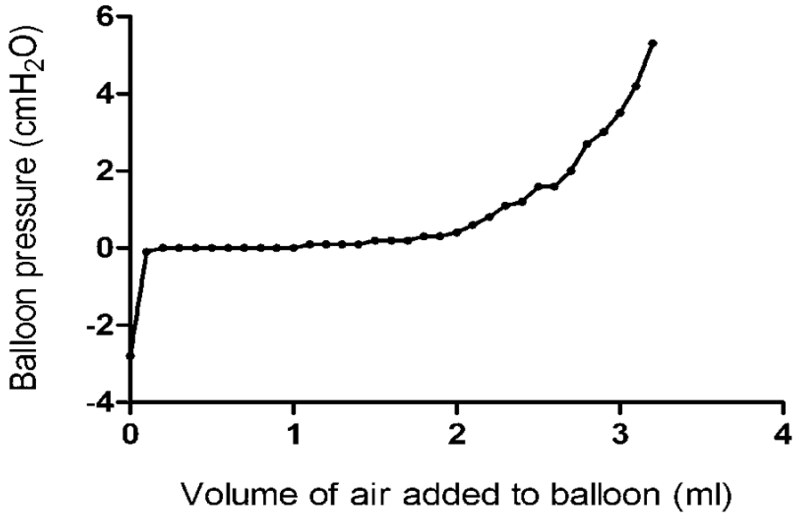
Topical anaesthetic with 10% lidocaine spray (Xylocaine, AstraZeneca, Luton, UK) was applied to the subject's nostril and oropharynx prior to insertion of the balloon catheters to reduce discomfort [246]. Lubricant gel (K-Y™, Johnson and Johnson, New Jersey, USA) was applied to both catheter tips to facilitate smooth insertion. With the head in a relaxed and neutral position, both the oesophageal and gastric balloon catheters were inserted simultaneously via one nostril and advanced past the hypopharynx and into the oesophagus and stomach whilst the subject swallowed sips of water through a straw. The catheters were inserted to a distance of 70 cm from the catheter tips to the level of the nostril, using the scale marked on the catheters as a guide. Verification of the position of both catheters within the stomach was verified by demonstrating a positive deflection in both P_{oes} and P_{ga} traces during a sniff manoeuvre. One catheter was then repositioned into the oesophagus by withdrawing the catheter to a distance of 40 cm. Verification of the position within the oesophagus was established by observing a change in sniff-related P_{oes} from positive to negative. The correct position of the oesophageal balloon was also confirmed by comparing P_{oes} and mouth pressure during an inspiratory effort against an occluded airway. P_{oes} and P_{mo} values within 10% of each other were considered indicative of accurate positioning [247]. The catheters were then securely taped to the subject's nose to ensure that their position was kept

constant and the pressure balloons inflated with air (0.5 ml into the oesophageal and 2 ml into the gastric balloon catheter) [231].

3.5.3 Pressure volume characteristics of the balloon catheter

The pressure-volume characteristics of the balloon catheter were tested to assess the elastic properties of the balloon and its contribution to measured P_{oes} and P_{ga} values [248]. This was determined by initially submerging the catheter under 5 cm of water to empty the balloon [249]. A 3-way tap at the proximal end of the balloon catheter was closed to the atmosphere to keep the system airtight and the catheter attached to a differential pressure transducer. The observed pressure within the balloon was then recorded whilst 0.1 ml aliquots of air were incrementally added via the 3-way tap to gradually fill the balloon [249]. As demonstrated in Figure 3-5, there was minimal change in observed pressure within the balloon between the operating ranges of inflation volumes used in this thesis (0.5 ml to 2.0 ml).

Figure 3-5 Pressure volume characteristics of the balloon catheter

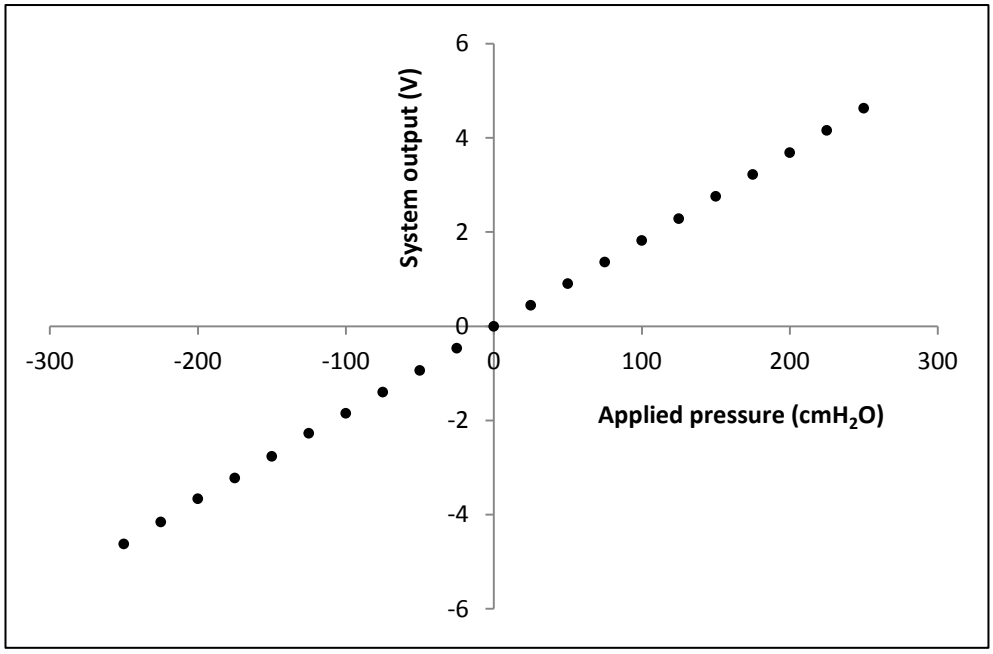


Laboratory experiment showing stable pressure measurements within the operating volume of the balloon catheter system (0.5 ml to 2.0 ml). Data provided in Appendix 1.

3.5.4 Linearity of the mouth pressure transducer system

The linearity of the mouth pressure transducer system was tested by applying known pressures using the digital manometer and plotting these against the P_{mo} system output. The mouth pressure transducer system had a linear response across a range of -250 to 250 cmH_2O (Figure 3-6).

Figure 3-6 Linearity of mouth pressure transducer system



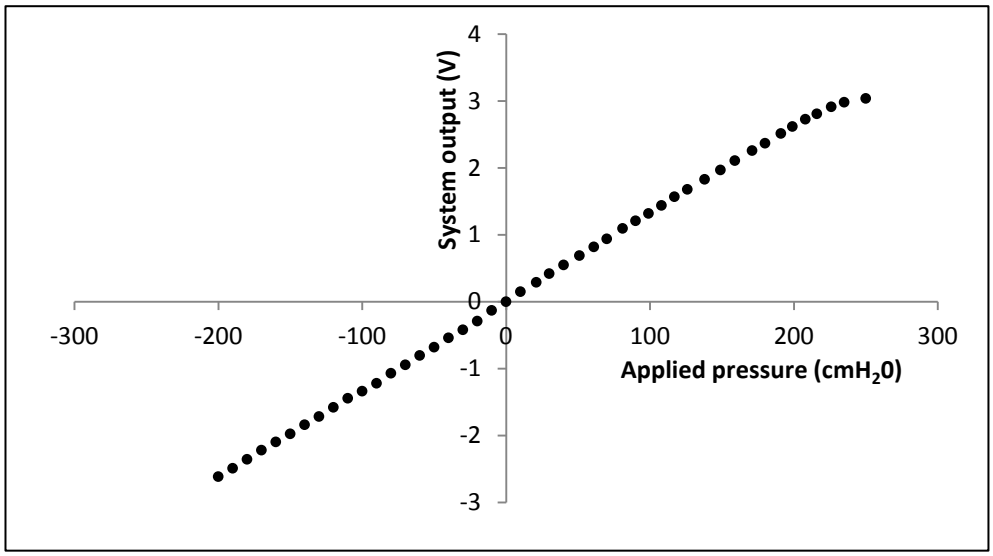
Laboratory experiment showing the linearity of the mouth pressure transducer system across a range of applied pressures. Data provided in Appendix 2.

3.5.5 Linearity of the oesophageal and gastric pressure transducer systems

The linearity of the oesophageal and gastric balloon catheter-pressure transducer-amplifier systems were tested by applying known pressures using the digital manometer to an airtight container in which the balloon catheter had been placed. The observed system output from the amplifier was plotted against the applied pressures. The oesophageal balloon catheter was inflated with 0.5 ml of air and the gastric balloon catheter was inflated with 2 ml of air.

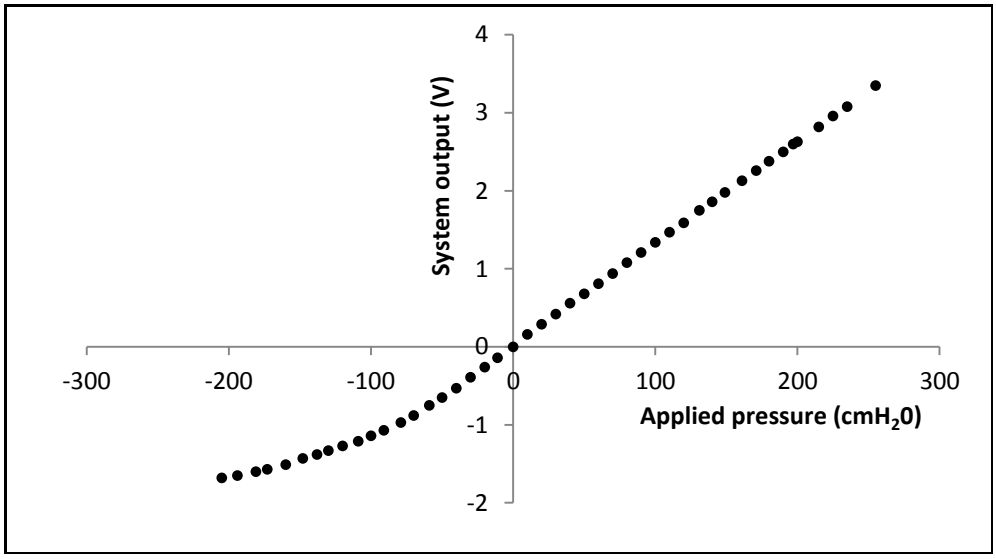
The oesophageal and gastric balloon catheters and their associated pressure transducers and amplifier were linear across the range of pressures recorded in this thesis. The oesophageal balloon catheter system was linear across the range -200 to 250 cmH_2O (Figure 3-7). As expected, the gastric balloon catheter system was linear across the desired operating positive pressure range, only becoming alinear at negative pressures in excess of 100 cmH2O (**Error! Reference source not found.**). ince pressures within the abdominal compartment are always positive, this limitation did not affect results.

Figure 3-7 Linearity of oesophageal balloon catheter system



Laboratory experiment showing the linearity of the oesophageal balloon catheter system across a range of applied pressures between -250 cmH_2O and 200 cmH_2O. Data provided in Appendix 3.

Figure 3-8 Linearity of gastric balloon catheter system



Laboratory experiment showing the linearity of the gastric balloon catheter system output across a range of applied pressure between -100 cmH_2O and 250 cmH_2O, but a non-linear response to negative applied pressures in excess of -100 cmH_2O. Data provided in Appendix 4.

3.5.6 Frequency response of the balloon catheter pressure transducer system

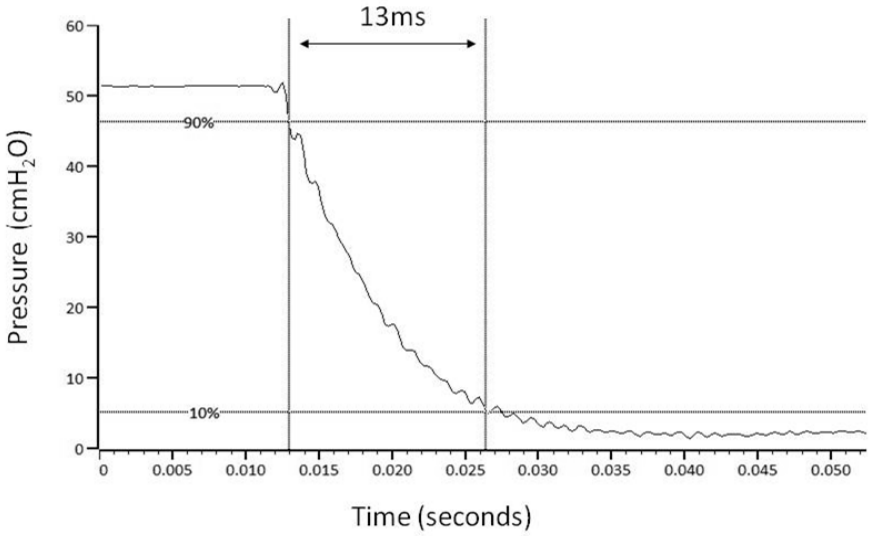
The ability of a measuring system to accurately detect and represent changes in the signal is known as its frequency response [250]. The "time constant" of the measuring system gives a measure of its dynamic response to an input step change and is related to the frequency response.

The frequency response of the mouth pressure transducer amplifier system was assessed by introducing a catheter (of the same length and diameter as that used to measure the mouth pressure) into a pressurised inflatable balloon and then measuring the response to a quasi-instantaneous change by bursting the balloon with a needle [250, 251]. As shown in Figure 3-9, the response time for the pressure signal to fall from 90% to 10% of baseline was 13 ms. Using the Fourier transformation equation, the frequency response (Fr) of the balloon catheter-transducer-amplifier system was:

Fr = $(3*0.013)^{-1}$ = 25.6 Hz.

This frequency response was sufficiently high to measure respiratory pressure waves [231, 236, 252].

Figure 3-9 Frequency response of balloon catheter system



Laboratory 'balloon pop test' experiment showing a response time of 13 ms for the observed pressure by the balloon catheter pressure transducer system to fall from 90% to 10% of baseline in response to a quasi-instantaneous change.

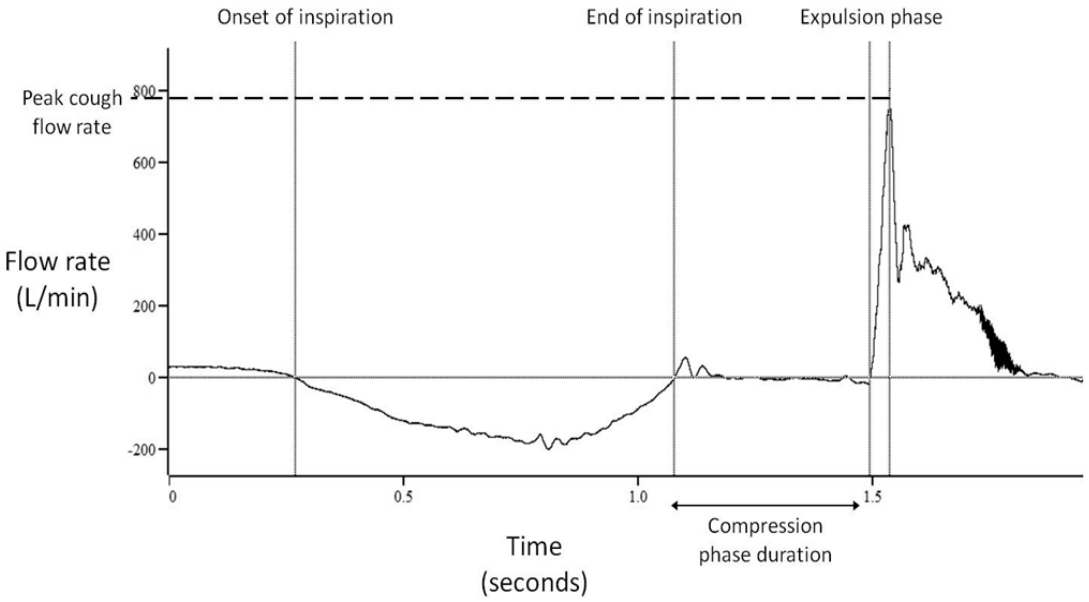
3.6 Measurement of flow

3.6.1 Measurement of cough flow rate and volumes

Respiratory flow was measured at the mouth using a Fleisch type pneumotachograph (Size 5, P.K. Morgan ltd, Kent, UK) attached to a full-face mask (Hans Rudolph Inc, Kansas City, USA). The pressure differential across the pneumotachograph was measured using a differential pressure transducer (DP45, Validyne, Northridge, CA, USA) and amplifier (CD280, Validyne, Northridge, CA, USA). The pneumotachograph was calibrated prior to each study by employing 2-point calibration using a rotameter (KDG Mobrev®, England).

Peak cough flow rate (PCFR), inspired volume (IV) and compression phase duration were calculated from the flow signal (Figure 3-10). PCFR was defined as the peak expiratory flow rate during a cough manoeuvre. IV was defined as the volume of air inspired prior to a cough expulsion, and was measured by integration of the respiratory flow signal between the onset and end of inspiration [211]. CPD was defined as the time between termination of inspiration (return to zero flow) and onset of expiration (departure from zero flow) [223]. To ensure standardisation, a custom software script was used to automatically place cursors at the onset and end of the inspiratory and compression phases. The accuracy of all cursor positions were verified manually prior to calculation of flow measures.

Figure 3-10 Respiratory flow trace during a cough manouevre

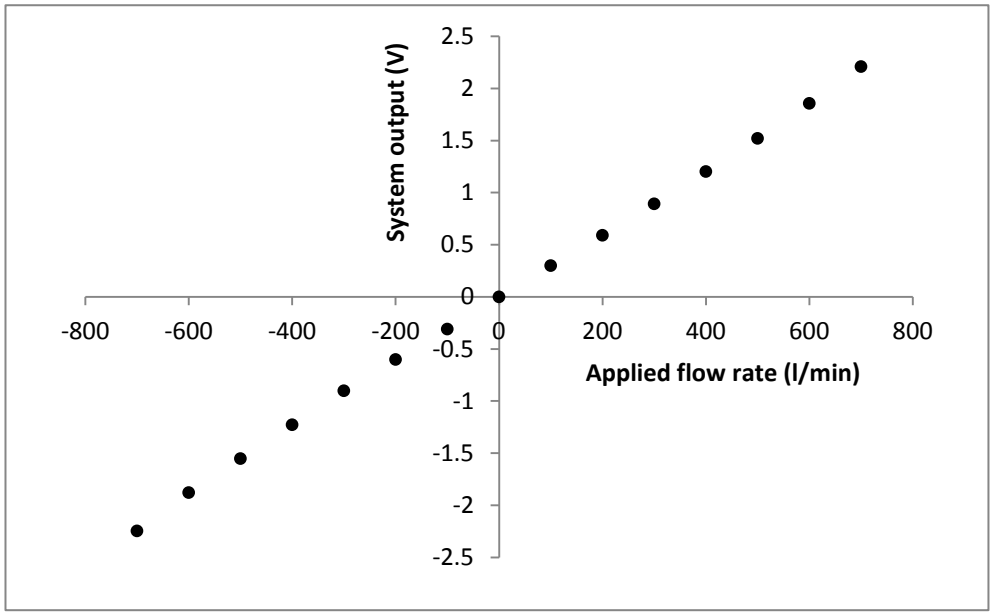


Flow signal during a voluntary cough manoeuvre in a healthy female subject.

3.6.2 Linearity of the pneumotachograph system

The linearity of the pneumotachograph-transducer-amplifier system was tested by applying a range of known flow rates using a rotameter (± 1000 L/min) and plotting these against the observed system output. The pneumotachograph-transducer-amplifier system was linear across the flow range ± 800 L/min (Figure 3-11).

Figure 3-11 Linearity of the pneumotachograph system



Laboratory experiment showing the linearity of the pneumotachograph system output across a range of applied flow rates between -800 L/min and 800 L/min. Data provided in Appendix 5.

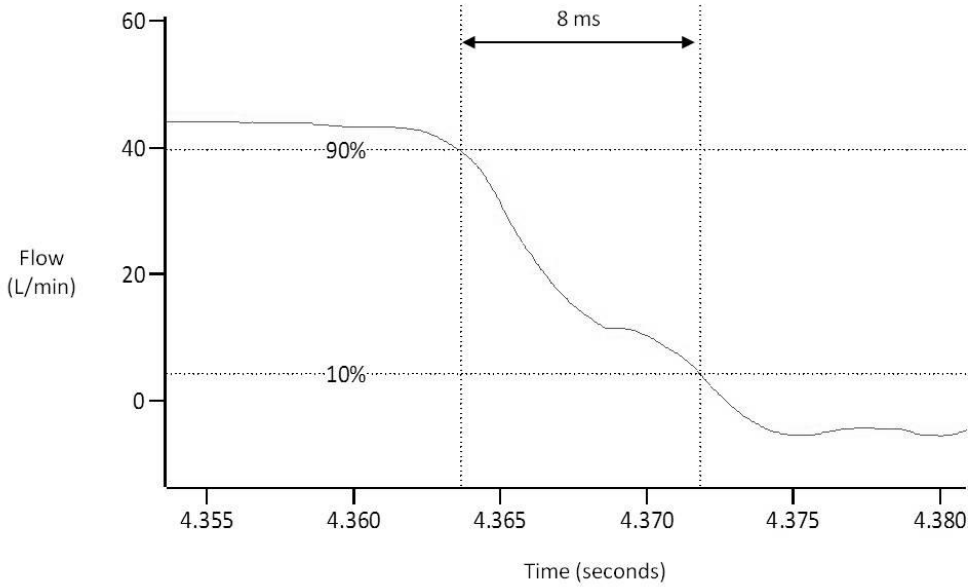
3.6.3 Frequency response of the pneumotachograph system

The frequency response of the pneumotachograph system was tested by using a pressurised inflatable balloon to deliver a constant flow rate through the pneumotachograph and then causing quasi-instantaneous cessation of flow by bursting the balloon with a needle. The response time for the fall in the flow signal from 90% to 10% of baseline was 8 ms (Figure 3-12). Using the Fourier transformation equation described in section 3.5.6, the frequency response of the pneumotachograph system was:

$Fr = (3*0.008)^{-1} = 41.7$ Hz.

This frequency response was sufficiently high to measure peak flow rates [242, 253].

Figure 3-12 Frequency response of pneumotachograph system

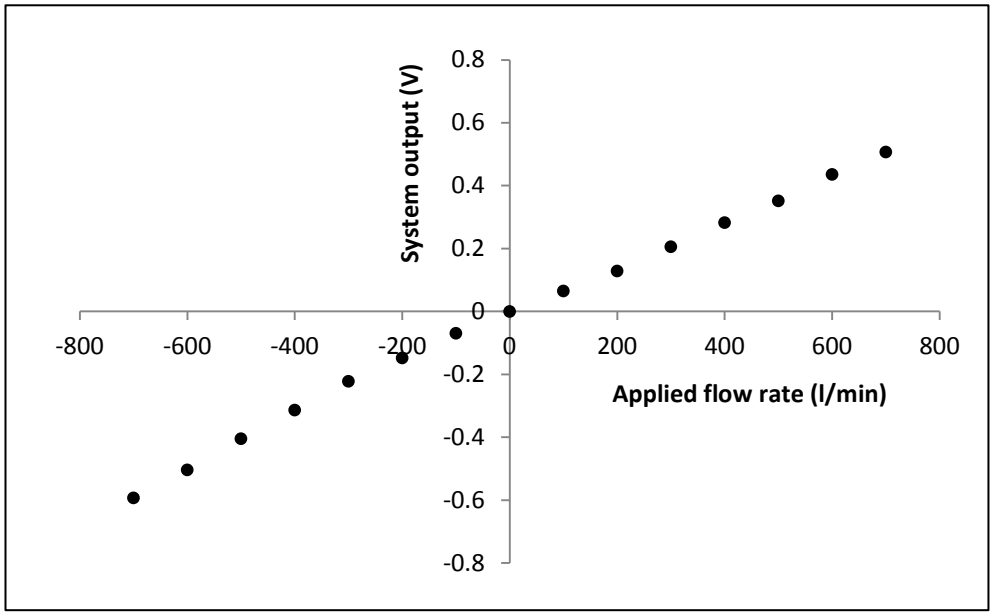


Laboratory 'balloon pop test' experiment showing a response time of 8 ms for the observed flow rate by the pneumotachograph system to fall from 90% to 10% of baseline in response to a quasi-instantaneous change.

3.6.4 Linearity of the pneumotachograph system after nebulisation of capsaicin

The linearity of the pneumotachograph-transducer-amplifier system was tested following ultrasonic nebulisation of capsaicin (see section 3.10) to assess the effect of nebulised particle deposition on the pneumotachograph. As shown in Figure 3-13, the pneumotachograph-transducer-amplifier system remained linear across the flow range ± 700 L/min after nebulisation of capsaicin.

Figure 3-13 Linearity of pneumotachograph system following capsaicin nebulisation



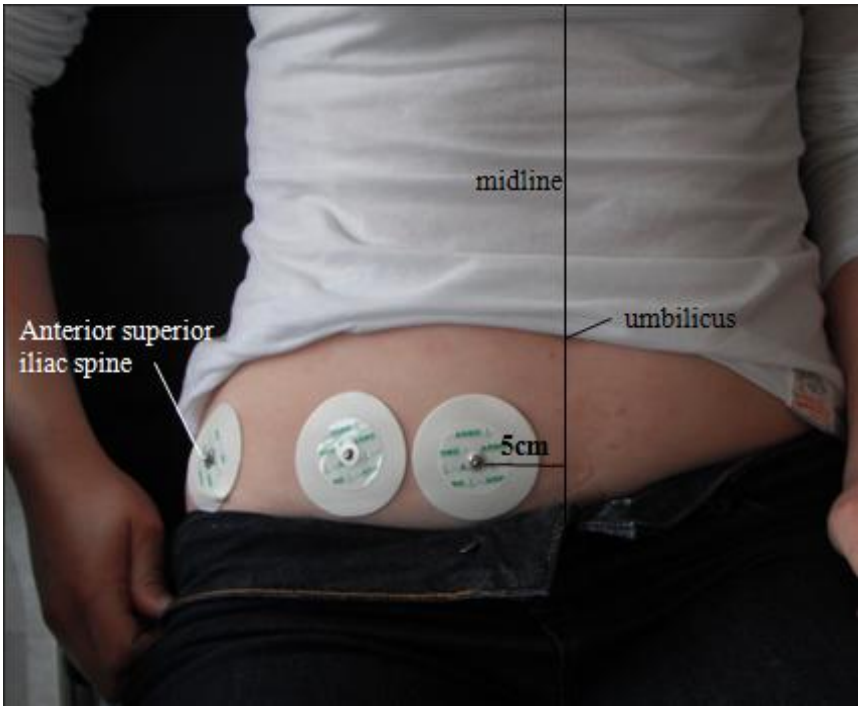
Laboratory experiment showing the maintained linearity of the pneumotachograph system following nebulisation of capsaicin during induced cough challenges. Data provided in Appendix 6.

3.7 Measurement of abdominal electromyography

3.7.1 Equipment and placement of EMG electrodes

Surface EMG was recorded from the right rectus abdominis muscle using 55 mm diameter Ag-AgCl electrodes (Kendall liquid gel electrodes, Tyco healthcare, Hampshire, UK). Prior to electrode attachment, the skin was thoroughly cleaned and lightly prepared using an abrasion gel (Nuprep abrasive skin gel, Weaver & Co, USA)[229]. The active electrode was placed 5 cm from the midline, just below the level of the umbilicus, and the reference electrode was placed 5 cm laterally [133]. The earth electrode was placed over the anterior superior iliac spine (Figure 3-14).

Figure 3-14 Placement of electrodes for abdominal electromyography



3.7.2 EMG signal processing

EMG signals were amplified and digitally filtered between 10 Hz and 2,000 Hz (1902 signal conditioner, Cambridge Electronic Design, Cambridge, UK). An additional 50 Hz notch filter was also applied to eliminate mains voltage background noise. Data

was sampled at a frequency of 5,000 Hz (Micro 1401 analogue to digital converter, Cambridge Electronic Design, Cambridge, UK), and displayed on a computer using Spike 2 software (Cambridge Electronic Design, Cambridge, UK).

3.7.3 EMG data analysis

The EMG signals from the abdomen were rectified by applying post-acquisition processing using Spike 2 software. The root mean square of the EMG signal was calculated with a 50 ms time window to give a moving average of the EMG activity [211, 214]. This resulted in 250 data points per 50 ms window, giving a smoother envelope of EMG activity for analysis [254]. Abdominal muscle EMG activity (EMG_{abdo}) was taken as the peak value of the root mean squared EMG trace for any given cough.

To allow collective group analyses, EMG data was normalised by expressing EMG_{abdo} for each cough as a fraction of the largest EMG_{abdo} observed during the maximum voluntary cough (MVC) protocol for that subject.

For comparisons of EMG_{abdo} during MVC between subjects, it was not possible to normalise to MVC since all values would be 1.0. In this case, EMG_{abdo} was normalised to that achieved during non-volitional lower thoracic nerve root magnetic stimulation at 100% stimulator output ($EMG_{abdo:Tw}$). Details of this manoeuvre are described in section 3.8.2. The resulting EMG activity seen from magnetic stimulation is the compound muscle action potential (CMAP).

3.8 Assessment of expiratory muscle function

3.8.1 Volitional assessment of expiratory muscle strength

The maximum expiratory mouth pressure ($P_{E,max}$) was measured as a volitional assessment of expiratory muscle strength [231]. Mouth pressure (P_{mo}) was recorded as described in section 3.5.1. Subjects were seated comfortably and instructed to insert the flanged mouthpiece attached to the metal tube into the mouth and form an airtight seal around the mouthpiece. With the shutter valve open, subjects were instructed to inhale to total lung capacity (TLC), at which point the shutter valve was closed, and then to exhale with maximum sustained force against the closed valve. The procedure was repeated until at least three $P_{E,max}$ measures were recorded and at least two were of consistent magnitude (within 10% error).

3.8.2 Non-volitional assessment of expiratory muscle strength

Gastric pressure was measured during lower thoracic nerve root magnetic stimulation as a non-volitional assessment of expiratory muscle contractility [111, 226, 255]. Stimulations were delivered using a double energy stimulator (Magstim Co Ltd, Dyfed, Wales) and a 90 mm circular coil.

Since the prior contractile history of a muscle can significantly affect the amplitude of the twitch response (twitch potentiation), subjects were rested for 20 minutes whilst refraining from talking or coughing prior to undertaking magnetic stimulation studies [217, 256]. Subjects were placed in the seated position and leant slightly forwards [255, 257]. All stimulations were performed with the subject relaxed and at end-expiration [111]. The level of the 9^{th} (T9), 10^{th} (T10) and 11^{th} (T11) thoracic vertebrae were marked on the skin with a pen. The optimal position of the coil for delivering stimulations was determined by delivering stimulations at T9, T10 and T11. The level which evoked the largest P_{ga} response to magnetic stimulation was defined as the optimal position [258]. This position was marked with indelible ink and used for all subsequent stimulations.

Gastric pressure elicited by magnetic stimulation (twitch gastric pressure, Twitch T_{10} P_{ga}) was measured from trough-to-peak of the P_{ga} trace and was determined from the average response to five stimulations [226].

Supramaximality of the magnetic stimulation procedure was assessed in subjects by measuring Twitch T_{10} P_{ga} and CMAP amplitude at stimulations of different power. Stimulator output was altered by 10% increments and delivered in a random order. Subjects were blinded to the stimulator power level. Supramaximality was defined as the absence of a significant difference in CMAP or Twitch T_{10} P_{ga} between 100% and 90% stimulator output [217, 259].

3.9 Measurement of cough sound

3.9.1 Equipment and acquisition of sound data

Cough sound was recorded using a free-field microphone (MKE 2-5-C, Sennheiser, Wedemark, Germany) and a contact microphone (3017, Philips Respironics, Surrey, UK). It was beyond the scope of this thesis to validate the frequency range of the microphones, but the free-field microphone has a reported frequency range of 20-20,000 Hz. The contact microphone was positioned anterolaterally over the larynx and fixated with a purpose made adhesive pad. The free-field microphone was fixed 15 cm inferiorly to the contact microphone in the midline.

3.9.2 Sound signal processing

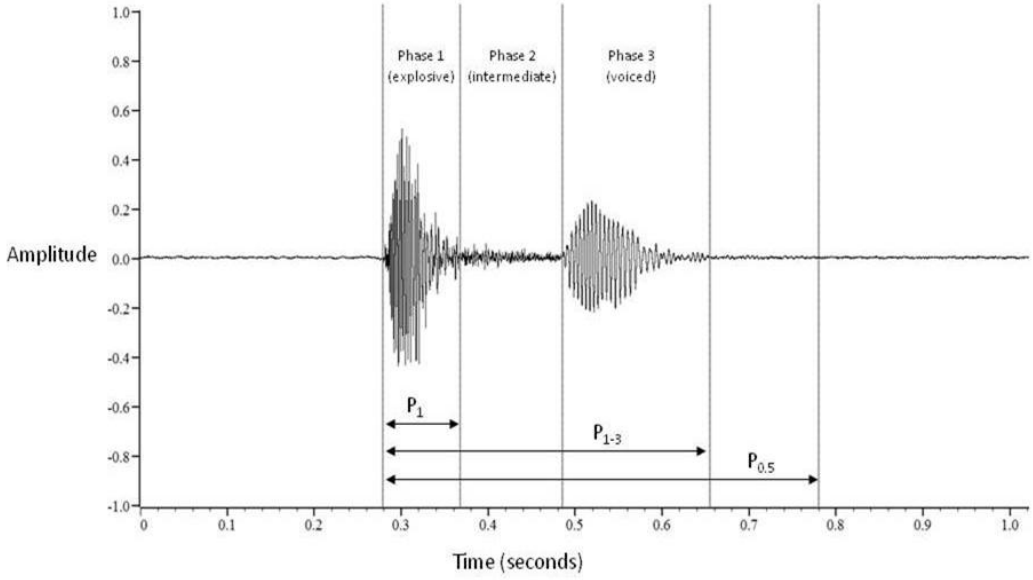
Signals from both microphones were acquired through a signal conditioner (1902, Cambridge Electronic Design, Cambridge, UK) and time-synchronised with physiological data via an analogue to digital converter (micro 1401 mk II, Cambridge Electronic Design, Cambridge, UK). Signals were sampled at a frequency of 8,000 Hz, amplified (free field microphone gain x10, contact microphone gain x3) and digitally filtered with a high pass filter of 10 Hz and a low pass filter of 4,000 Hz. A 50 Hz notch filter was applied to eliminate background mains voltage noise.

3.9.3 Cough sound data analysis

Each cough sound signal was divided into its component phases: the explosive phase (phase 1), the intermediate phase (phase 2) and, if present, the voiced phase (phase 3) (Figure 3-15). All cough sounds contain a phase 1 segment, but not all sounds contain a voiced phase. In order to maximise consistency, the start and end of the each phase was identified by a custom automated script using Spike 2 software (Cambridge Electronic Design, Cambridge, UK) before manual confirmation. A further labelling cursor was placed precisely 0.5 seconds after the onset of phase 1. From preliminary analysis, reliable demarcation of the end of phase 2 can be difficult for coughs without a phase 3 segment due to the gradual dissipation of the sound signal towards baseline. Therefore, cough sound parameters were calculated for the following time-windows: from onset to end of

phase 1 (P_1), from onset of phase 1 to end of phase 3 (the whole cough sound, P_{1-3}) and a 0.5-second duration from onset of phase 1 ($P_{0.5}$).

Figure 3-15 A typical 3-phase cough sound signal



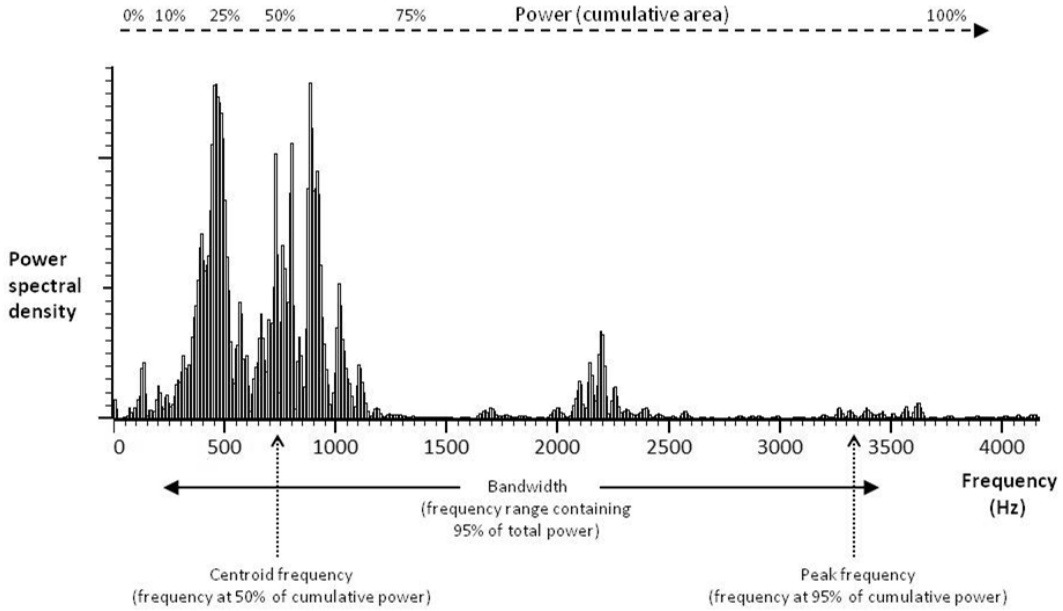
Phases of a 3-phase cough sound signal and time-windows chosen for analysis. Trace is of a voluntary cough manoeuvre in a female patient with chronic cough. P_1: phase 1 time window; P_{1-3}: phases 1-3 time window; $P_{0.5}$: 0.5 second time window.

Each time window was analysed using a custom script for MATLAB® software (The MathWorks Inc, Massachusetts, USA) to calculate the following parameters: total power (PW), peak energy (Ep), mean energy (Em), rise time (RT), duration (D), bandwidth (BW), peak frequency (Fp) and centroid frequency (Fc).

The time domain parameters (Ep, Em, RT and D) were calculated from the root mean square (RMS) of the sound signal and the frequency domain parameters (PW, BW, Fp and Fc) were derived from the frequency spectrum profile [194, 260]. The RMS envelope was calculated using 32-point (4 ms) windows with 50% overlap and the frequency spectrum, or power spectral density (PSD), was calculated using 8,000-point Fast Fourier Transformation (FFT) of the sound signal [187, 194]. A graphical presentation of a sample sound signal presented in the frequency

spectrum is shown in Figure 3-16. The definitions of the sound parameters are described in detail in section 7.4.3.

Figure 3-16 Cough sound signal displayed in the frequency spectrum



Cough sound signal displayed in the frequency spectrum following Fast Fourier Transformation. The trace above is the transformed signal of the cough shown in Figure 3-15, acquired in a female patient with chronic cough.

3.10 Induced cough challenges

Induced coughs were evoked by using capsaicin cough challenges [79]. Capsaicin induces cough in a dose-dependent manner and the challenge tests are safe and reproducible [261-263]. The capsaicin solution concentrations required ranges from 0.49 µM to 10,000 µM [208].

3.10.1 Capsaicin preparation and storage

Capsaicin (8-Methyl-N-Vanillyl-6-Nonenamide) has a molecular mass of 305 Daltons and therefore 305 g of capsaicin in 1 litre of fluid yields a solution concentration of 1 M or 1,000,000 µM. A 'stock solution' containing 10 ml of 10,000 µM capsaicin was prepared by dissolving 0.03054 g (30.5 mg) of capsaicin (Sigma-Aldrich, Missouri, USA) in 1 ml of 100% ethanol (Absolute alcohol 100, Hayman Ltd, Witham, Essex, UK), 1 ml of Tween® 80 (Sigma-Aldrich, Missouri, USA) and 8 ml of physiological saline [264]. A high sensitivity scale (SBA32, Scaltec instruments, Heiligenstadt, Germany) was used to measure the capsaicin. 1 ml of stock solution was then diluted with 9 ml saline to produce a solution with a concentration of 1,000 µM. Further serial doubling dilutions with saline produced solutions with capsaicin concentrations ranging from 0.49 µM to 1,000 µM (Table 3-1) [79, 264].

Capsaicin stock solution was kept for a maximum of 4 weeks at 4^{o}C and shielded from light [265]. Solutions for nebulisation were freshly prepared on the day of each study [79].

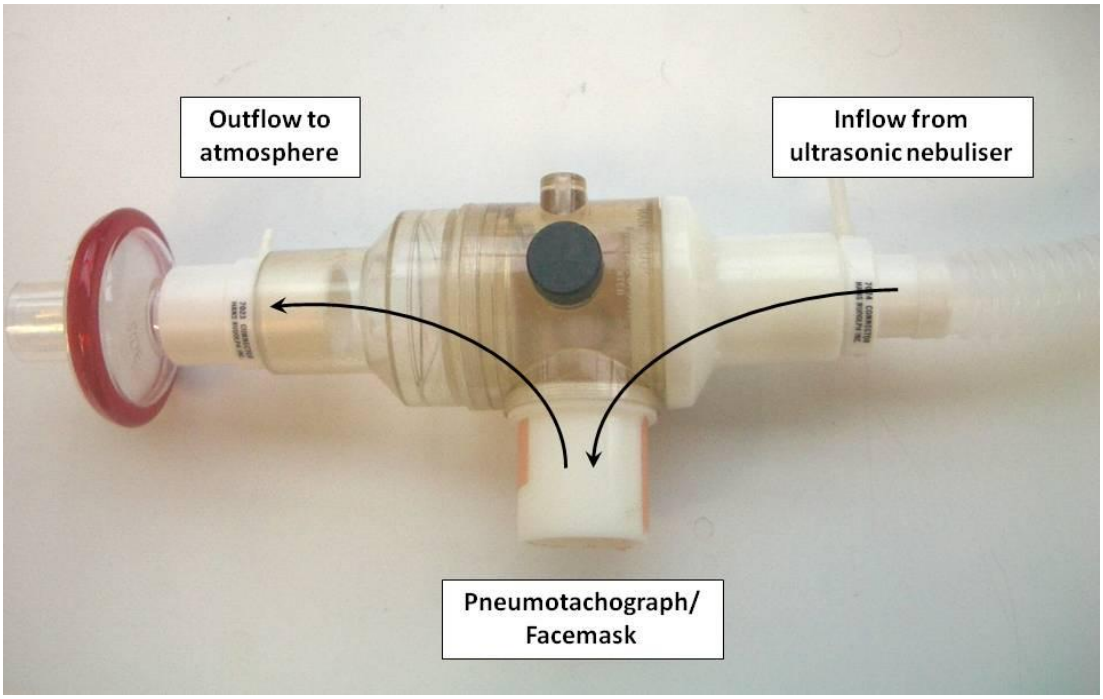
Table 3-1 Serial dilution of capsaicin stock solution for induction of reflex coughs

Initial concentration	Volume of capsaicin solution	Added volume of saline	Final concentration
10,000 µM (stock)	1 ml	9 ml	1,000 µM
1,000 µM	5 ml	5 ml	500 µM
500 µM	5 ml	5 ml	250 µM
250 µM	5 ml	5 ml	125 µM
125 µM	5 ml	5 ml	62.5 µM
62.5 µM	5 ml	5 ml	31.25 µM
31.25 µM	5 ml	5 ml	15.6 µM
15.6 µM	5 ml	5 ml	7.8 µM
7.8 µM	5 ml	5 ml	3.9 µM
3.9 µM	5 ml	5 ml	1.95 µM
1.95 µM	5 ml	5 ml	0.98 µM
0.98 µM	5 ml	5 ml	0.49 µM

3.10.2 Equipment and administration of capsaicin

Capsaicin was administered in aerosolised form using an ultrasonic nebuliser (U3000, DeVilbiss Healthcare, Wollaston, UK). Subjects inhaled the nebulised capsaicin through a facemask attached to a valve box (Hans Rudolph Inc, Kansas City, USA). The nebuliser efferent tubing was connected to the inflow port of the valve box and a particle filter was attached to the outflow port to prevent dispersion of nebulised capsaicin into the open atmosphere (Figure 3-17). The valve box permitted uni-directional flow from the ultrasonic nebuliser to the subject on inspiration and uni-directional flow from the subject to the atmosphere on expiration, whilst allowing measurement of bi-directional flow at the mouth with a pneumotachograph.

Figure 3-17 Capsaicin nebulisation circuit valve box



A valve box was used during capsaicin cough challenges to allow uni-directional flow of nebulised capsaicin from the ultrasonic nebuliser whilst permitting bi-directional measurement of airflow at the mouth with a pneumotachograph.

3.10.3 Protocol

The tidal breathing method over a 1-minute period was employed rather than the single breath method, as this allowed continuous measurement of cough flow rates with a pneumotachograph during induced coughs [4, 266]. Subjects underwent nebulisation with saline control solution prior to administration of capsaicin solutions. Increasing incremental concentrations of aerosolised capsaicin were then administered, beginning with the lowest concentration, 0.49 µM. Subjects were blinded to the protocol order. Placebo nebulisations with physiological saline were randomly interspersed with capsaicin nebulisations [208]. Each nebulisation was delivered for 1 minute, with 2-minute intervals between concentrations [219]. Subjects were instructed to maintain resting tidal breathing and to refrain from suppressing coughs [208]. The number of coughs induced by each capsaicin concentration nebulisation was counted. The lowest concentration inducing 5 or

more coughs was defined as C_5, and the supra-C_5 threshold was defined as the next concentration increment that reproduced at least 5 coughs. Supra-threshold challenges were performed since reproducibility of some cough measures such as cough frequency and time to cough have been shown to be superior with higher stimuli [215]. Capsaicin challenges continued until supra-threshold concentration was established. If the subject was unable to tolerate the threshold concentration, the supra-threshold concentration was not given.

3.11 Measurement of cough frequency

3.11.1 Objective cough frequency monitoring

Cough frequency was measured using the Leicester Cough Monitor (LCM) [173]. It consists of an MP3 sound recording device (662 Digital Voice Tracer, Philips, UK) that records and stores sound data obtained from a lapel microphone (Figure 3-18). Details on the performance of the LCM have been described in section 1.4.2. Subjects were set up with the LCM system in the laboratory and then instructed to return to their usual daily activities within their own environment. The LCM was returned for analysis after 24 hours of monitoring.

Figure 3-18 Leicester Cough Monitor system recorder

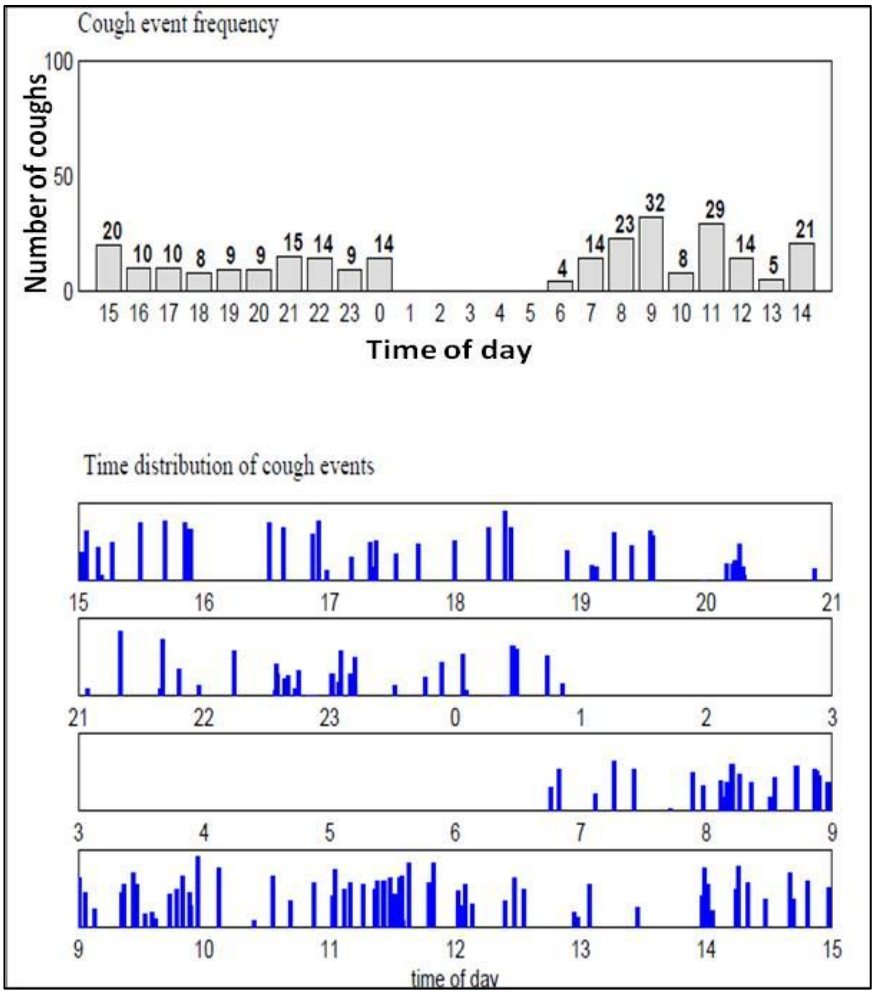
The Leicester Cough Monitor recording system comprises of an MP3 recording device and a free-field microphone.

3.11.2 Cough frequency data analysis

The cough monitoring data was analysed on a computer using semi-automated custom LCM software, based on Hidden Markov Model speech recognition algorithms [171, 172]. Coughs are detected as single events whether occurring in

isolation or within bouts of coughs. Candidate cough events are automatically detected by the software and a sample of 50-100 candidate cough events are verified by an operator in order to refine the cough detection algorithm (see section 1.4.2 for further details). The LCM cough frequency report presents data as the number of coughs detected in each hour of the 24-hour monitoring period (Figure 3-19).

Figure 3-19 Leicester Cough Monitor system report



Example of a 24-hour cough frequency report from the Leicester Cough Monitor system. The above example was acquired in a female patient with chronic cough.

3.12 Acquisition, analysis and storage of data

All acquired physiological and sound data were time synchronised and converted from analogue to digital format (Micro 1401 mk II, Cambridge Electronic Design, Cambridge, UK) and then recorded, stored and analysed on a computer (Dell Corporation Ltd, Berkshire, UK) using Spike 2 software version 6.14 (Cambridge Electronic Design, Cambridge, UK). Cough frequency data was transferred from the LCM to a computer (Dell Corporation Ltd, Berkshire, UK) for storage and analysis using custom software as described above.

3.13 Statistical analysis

Statistical analysis of the data was performed using Prism® v5.0 for Windows (GraphPad) and SPSS 19.0 for Windows (IBM). All data was tested for normality distribution using the D'Agostino and Pearson omnibus normality test prior to performing statistical analyses. A p-value of less than 0.05 was considered as indicative of statistical significance. A variety of statistical tests is used in this thesis and these are discussed in more detail in the relevant chapters.

4 A longitudinal assessment of acute cough

This chapter was submitted in manuscript form and accepted for publication. Reference:

Lee KK, Matos S, Evans DH, White P, Pavord ID, Birring SS. A longitudinal assessment of acute cough. American Journal of Respiratory and Critical Care Medicine 2013;187(9):991-997

4.1 Abstract

Rationale: Cough can be assessed with visual analogue scales (VAS), health status measures, and 24-hour cough frequency monitors (CF_{24}). Evidence for their measurement properties in acute cough caused by upper respiratory tract infection (URTI) and longitudinal data is limited.

Objectives: To assess cough longitudinally in URTI with subjective and objective outcome measures and determine sample size for future studies.

Methods: Thirty-three previously healthy subjects with URTI completed cough VAS, Leicester Cough Questionnaire (LCQ-acute), and CF_{24} monitoring (Leicester Cough Monitor) on three occasions, 4 days apart. Changes in subjects' condition were assessed with a global rating of change questionnaire. The potential for baseline first-hour cough frequency (CF_1), VAS, and LCQ to identify low CF_{24} was assessed.

Measurements and Main Results: Mean ± SD duration of cough at visit 1 was 4.1 ± 2.5 days. Geometric mean ± log SD baseline CF_{24} and median (interquartile range) cough bouts were high (14.9 ± 0.4 coughs/h and 85 (39–195) bouts/24 h). Health status was severely impaired. There was a significant reduction in CF_{24} and VAS, and improvement in LCQ, from visits 1–3. At visit 3, CF_{24} remained above normal limits in 52% of subjects. The minimal important differences in CF_{24}, LCQ, and VAS were 54%, 2.0 and 17 mm changes from baseline, respectively. The sample sizes required for parallel group studies to detect these changes are 27, 51, and 25 subjects per group, respectively. CF_1 (<20.5 coughs/h) was predictive of low CF_{24}.

Conclusions: CF_{24}, VAS, and LCQ are responsive outcome tools for the assessment of acute cough. The minimal important difference in cough frequency is 54%. The sample sizes required for future studies are modest and achievable.

4.2 Introduction

Acute cough due to upper respiratory tract infection (URTI) is the most common reason why patients seek medical attention [267]. It can be disruptive to the individual and is often associated with absence from work and lost productivity [6, 12, 20]. More than $3 billion dollars are spent on over the counter cough and cold remedies each year in the USA [24]. The efficacy of antitussive medications has recently been questioned by the American College of Chest Physicians cough guidelines and the findings of a meta-analysis [25, 268]. There is a pressing clinical need to develop effective antitussive drugs.

The severity of cough is thought to be determined by the frequency of coughs, their intensity and the impact on health status [137]. Assessment of cough severity can be performed using global measures such as visual analogue scales (VAS) or with tools measuring the individual components such as recently developed cough frequency monitors [52, 269]. The impact of cough on health related quality of life can be assessed with health status questionnaires. Little is known about the severity of cough in URTI particularly that assessed with objective tools such as cough frequency monitors. Furthermore, there is a paucity of longitudinal studies investigating cough severity and the natural history of URTI. A better understanding of the severity of cough in URTI will facilitate clinical interpretation of studies evaluating antitussive therapy.

4.3 Aims

The aim of this study was to investigate longitudinal cough frequency and other measures of cough severity in URTI, evaluate the magnitude of change important to patients and determine sample sizes necessary for future clinical studies. Some of the results of this study have been previously reported in the form of an abstract [270].

4.4 Methods

4.4.1 Subjects

Healthy volunteers with cough due to URTI of less than 10 days duration were recruited using advertisement posters or referred by their general practitioner during a 15-month period spanning two cold seasons (January 2010 to April 2011). Subjects with chronic cough, lung disease, current smoking history, symptoms suggestive of bacterial infection, or those taking angiotensin converting enzyme inhibitor, anti-histamine or antitussive medications were excluded. All subjects gave informed consent and the study was given ethical approval (East London and the City Research Ethics Committee 10/H0703/6).

4.4.2 Cough frequency monitoring

Objective 24-hour cough frequency (CF_{24}) was recorded using the Leicester Cough Monitor (LCM), a validated ambulatory cough monitoring system which has been used in randomised controlled trials of therapy for patients with chronic cough [88, 170, 173, 176]. Briefly, the LCM consists of a MP3 sound recording device (Philips LFH0662/LFH0865), external microphone (Philips LFH9173/Olympus ME-15) and automated cough detection software that requires minor operator input for calibration. Cough frequency was determined by counting all cough events individually, whether occurring in isolation or within coughing bouts. Cough bouts were defined as periods of continuous coughing, with pauses of <2 seconds [120]. Subjects were instructed to resume normal daily activities in their own environment during cough monitoring. Further details of the LCM and the cough detection algorithm have been described elsewhere [172, 173]. CF_{24} was expressed as the average number of coughs/hour over a 24-hour period. Cough bouts were expressed for 24-hour periods.

4.4.3 Questionnaires

Cough-specific, health related quality of life was assessed with the Leicester Cough Questionnaire (LCQ-acute), a 19-item questionnaire that has been validated in acute and chronic cough [11, 148]. The overall score ranges from 3 to 21 with a

higher score indicating a better quality of life. Subjective cough severity was assessed with a 100 mm cough visual analogue scale. Change in cough between visits was assessed with the Global Rate of Change Questionnaire (GRCQ) which was used to estimate clinically important changes in cough outcome parameters at visit 2 [245]. The response scale ranged from -7 (a great deal worse) to +7 (a great deal better) and the scores were categorised as *no change* (-1,0,+1), *small change* (-2,-3,+2,+3), *moderate change* (-4,-5,+4,+5) or *large change* (-7,-6,+7,+6) accordingly.

4.4.4 Protocol

Subject characteristics and symptoms at baseline were recorded. Subjects underwent objective 24-hour cough frequency monitoring at 3 time points during their illness: **Visit 1** (recruitment), **Visit 2** (visit 1 + 4 days) and **Visit 3** (visit 1 + 8 days). Subjects also completed LCQ and cough VAS at each visit and the GRCQ at visit 2. Cough frequency monitoring was commenced at a similar time of day for each visit. Subjects were instructed to refrain from taking antitussive drugs throughout the study period.

4.4.5 Analysis

SPSS version 19 (IBM) and Prism version 5 (GraphPad) were used for statistical analysis. Appropriate parametric or non-parametric tests were applied depending on data distribution. Cough frequency data were log-transformed to achieve normal distribution if appropriate. The upper limits of normal cough frequency in females and males were determined from a previous study, 5 and 2 coughs/hour respectively [175]. GRCQ scores were converted to absolute numbers, i.e. when the change was negative, the sign was reversed as was the sign of the corresponding change in VAS, LCQ and CF_{24} between visits [245]. Minimal important differences were calculated at visit 2 and were defined as the changes in CF_{24}, LCQ and VAS in subjects reporting a small change in GRCQ score. The determinants of 24-hour frequency at baseline (visit 1) and change in cough frequency (visits 1-2) were evaluated by univariate analysis of gender, duration of cough, VAS and LCQ. A longitudinal measure of cough frequency, LCQ and VAS from visits 1 to 3 was determined by calculating the area under the curve (AUC) for each subject and

dividing by the duration of the study. Sample sizes were calculated using G*Power version 3.1.2 (Faul) to detect the smallest clinically important change (between visits 1 and 2) for both linear and AUC outcome parameters. Sample size calculations based on AUC data will account for change in cough severity in addition to natural recovery. Sample sizes were also determined by a responder analysis between visits 1 and 2 using Fisher's exact test. A responder was defined as a subject whose cough improved greater than the smallest clinically important change. The predictive value of baseline LCQ, cough VAS and CF_1 for identifying subjects with low CF_{24} rates (≤10 coughs/hr) was assessed by plotting receiver operating characteristic (ROC) curves and calculating the AUC, sensitivity, specificity, negative predictive value and positive predictive value for each screening tool. A high sensitivity for identifying low frequency coughers was considered desirable.

4.5 Results

33 subjects (21 female) were included in the final analysis. The reasons for excluding subjects at screening are given in Figure 4-1. Baseline subject characteristics are given in Table 4-1.

Figure 4-1 Study recruitment

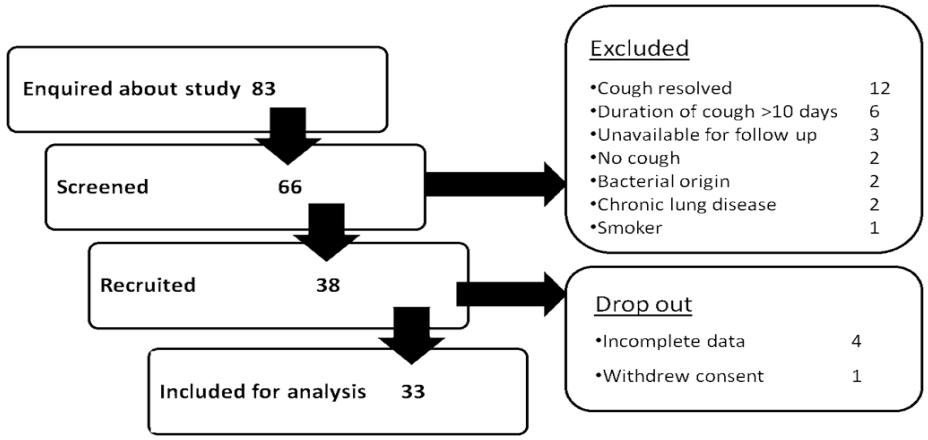


Table 4-1 Baseline characteristics

Characteristic	Value
Age (years)	31 (23-37)
Male:Female (n)	12:21
Smokers (%)	0
Cough duration to presentation (days)	4.1 ± 2.5
Rhinorrhoea (%)	82
Sneezing (%)	82
Headache (%)	69
Sore throat (%)	67
Coloured sputum (%)	50
Clear sputum (%)	33
Aches and pains (%)	31
Tiredness (%)	31
Fever (%)	27
Facial pain (%)	15
LCQ score	14.3 (11.0-18.1)
Cough VAS (mm)	46.0 (32.5-58.0)
CF_{24} (coughs/hr)*	14.9 ± 0.4
Cough bouts/24-hours	85 (39-195)

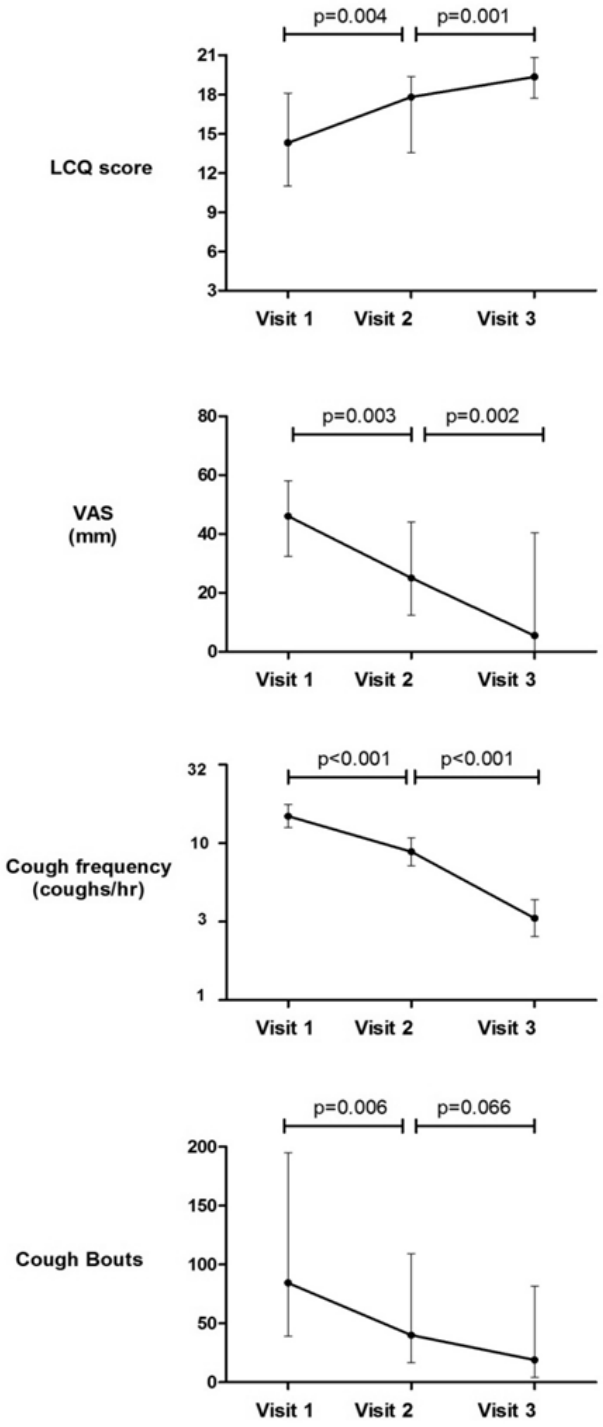
*Data presented as median (IQR), mean ± SD, n or %. *: geometric mean ± log SD. LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale; CF_{24}: 24-hour cough frequency.*

4.5.1 Natural course of acute cough

The mean ± standard deviation (SD) time from onset of cough to visit 1 was 4.1 ± 2.5 days. Geometric mean ± log SD 24-hour cough frequency at baseline was 14.9 ± 0.4 coughs/hr. The median (IQR) number of cough bouts in 24 hours at baseline was 85 (39-195) bouts. Cough specific quality of life was impaired at baseline; median (IQR) LCQ score was 14.3 (11.0-18.1). There was a significant reduction in cough frequency, cough bouts and VAS from visits 1 to 3, and improvement in health status (Figure 4-2). The geometric mean ± log SD 24-hour cough frequency at visit 2 and 3 was 8.8 ± 0.5 (41% reduction from baseline) and 3.3 ± 0.7 coughs/hr (78% reduction from baseline) respectively. The median (IQR) coughs per bout at visits 1-

3 were 2.7 (2.3-3.0), 2.7 (2.2-3.0) and 2.5 (2.1-2.9) coughs respectively (p=0.07, visits 1-3). Cough frequency decreased from visit 1 to visit 2 in 73% of patients and was unchanged or increased in the remainder. In subjects whose cough frequency decreased from visit 1 to visit 2, the magnitude of change in cough frequency was not associated with duration of cough (p=0.72), baseline LCQ (p=0.36), baseline cough VAS (p=0.10) or baseline cough frequency (p=0.80). There were no significant differences in baseline characteristics or cough severity between subjects whose cough improved and deteriorated between visits. At visit 3, 52% of subjects still had cough frequency above normal limits. The geometric mean ± log SD AUC/day for cough counts and median (IQR) AUC for LCQ and VAS were 248 ± 0.43 coughs, 16.6 (14.7-19.3) and 26 (18-43) mm respectively.

Figure 4-2 Longitudinal changes in quality of life, subjective cough severity and objective 24-hour cough frequency



LCQ, cough VAS and cough bouts data presented as median (IQR); cough frequency data presented as geometric mean (SEM); LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale.

4.5.2 Relationship between subjective and objective cough outcome measures in acute cough

There was a significant relationship between objective cough frequency and LCQ and cough VAS at visits 2 and 3 but not at visit 1 (Table 4-2). There was also a significant correlation between change in cough frequency and change in LCQ and cough VAS (Table 4-2).

Table 4-2 Relationship between subjective and objective measures of cough severity in acute cough

	Cough Frequency (CF_{24}, cough bouts)			**Δ Cough Frequency (CF_{24}, cough bouts)**	
	Visit 1	Visit 2	Visit 3	Visit 1-2	Visit 2-3
LCQ	-0.23, -0.23	-0.48†, -0.46*	-0.63‡, -0.62‡		
VAS	0.03, 0.09	0.42*, 0.59‡	0.69‡, 0.75‡		
Δ LCQ				-0.55*, -0.56†	-0.62‡, -0.57†
Δ VAS				0.51*, 0.45*	0.66‡, 0.70‡

Data presented as correlation coefficients. *: p<0.05; †: p<0.01; ‡: p<0.001. CF_{24}: 24-hour cough frequency (efforts per hour); cough bouts: number of coughing bouts in 24 hours; LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale; Δ: change.

4.5.3 Determinants of cough frequency

Female subjects coughed more frequently than men (geometric mean cough frequency AUC 309 vs. 168 coughs; mean fold difference 1.8; 95% CI 0.3 to 3.4; p=0.022). AUC cough severity VAS and LCQ were similar in both genders (p=1.0 and 0.9 respectively). The relationship between age and cough outcome measures was not assessed due to the narrow age range of subjects. There was no significant relationship between cough frequency and duration of cough (p=0.16), VAS (p=0.85), LCQ (p=0.28) or presence of other URTI symptoms at presentation such as fever and myalgia (p=0.16 - 0.95). There was no difference in LCQ or VAS in subjects with and without non-cough URTI symptoms (p=0.05 - 0.94). 33% of subjects had

baseline 24-hour cough frequency rates ≤10 coughs/hr. Both LCQ and cough VAS score at baseline were poor at identifying low frequency coughers; the AUC of the ROC curves for LCQ and VAS were 0.61 and 0.56 respectively. The geometric mean ± log SD CF_1 was 23.8 ± 0.4 coughs/hr. The AUC of the ROC curve for cough frequency during the first hour (CF_1) to detect low frequency coughers was 0.86. A threshold of CF_1 < 20.5 coughs/hr had a sensitivity and specificity of 91% and 77% respectively for predicting low 24-hour cough frequency. The sensitivities and specificities for a range of CF_1 thresholds are listed in Table 4-3.

Table 4-3 Predictive value of first hour cough frequency for detection of low frequency 24-hour cough counts

CF_1 threshold (coughs/hr)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<16.5	64	86	70	83
<19.0	82	82	69	90
<20.5	91	77	67	94

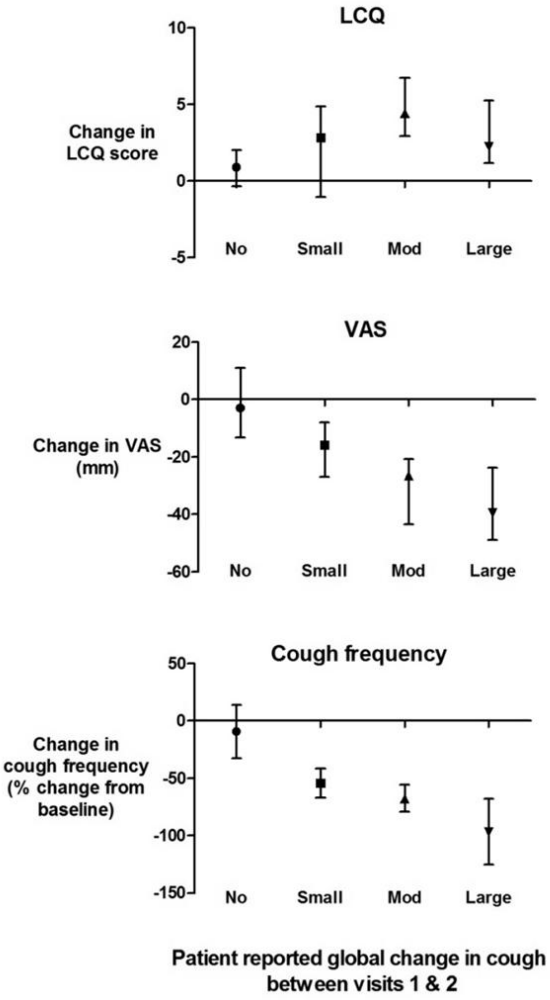
CF_1: cough frequency in the first hour; PPV: positive predictive value; NPV: negative predictive value.

4.5.4 Sample size calculations for future studies

In patients reporting a small change in GRCQ at visit 2, the change in CF_{24}, LCQ score and cough VAS were a 54%, 2.0 and 17 mm change from baseline respectively (Figure 4-3). The geometric mean ± log SD cough frequency for these patients at visits 1 and 2 were 24.2 ± 0.4 and 12.6 ± 0.4 coughs/hr respectively; mean fold difference 1.9; 95% CI 1.0 to 3.7; p=0.049. The number of subjects required for a parallel group study design to demonstrate a 54%, 2.0 and 17 mm change in CF_{24}, LCQ and VAS from visit 1 to 2 (i.e. a change from baseline) with 80% power (alpha level (α) of 0.05) were 26, 50 and 22 per group respectively. The number of subjects required for a parallel group study design to demonstrate a 54%, 2.0 and 17 mm change in AUC (i.e. a change in addition to that with natural recovery) for CF_{24}, LCQ and VAS with 80% power (α=0.05) were 27, 51 and 25 per group respectively.

Responders were defined as patients whose cough frequency, LCQ and VAS reduced by ≥ 54%, 2.0 and 17 mm respectively between visits 1 and 2. 42%, 52% and 55% of subjects responded between visits 1-2 (for cough frequency, LCQ and VAS respectively). The sample sizes required to detect an additional 20%, 30% and 40% responders are presented in Table 4-4.

Figure 4-3 Minimal important differences in LCQ, cough visual analogue scale and 24-hour cough frequency in acute cough



LCQ and cough VAS data presented as median (IQR); cough frequency data presented as geometric mean (SEM). LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale.

Table 4-4 Sample size calculations

	Change from baseline (visits 1-2)	AUC (visits 1-3)	Responder Analysis (additional response rate)		
			20%	30%	40%
Cough frequency	26	27	102	48	28
LCQ	50	51	101	43	22
VAS	22	25	98	41	20

Sample sizes are per group for a parallel study design. Sample sizes are calculated with 80% power and alpha level of 0.05 to demonstrate minimal important differences: 54%, 2.0 and 17 mm change in 24-hour cough frequency, Leicester Cough Questionnaire (LCQ) and visual analogue scale (VAS) respectively.

4.6 Discussion

In this study, longitudinal changes in cough frequency, health status and cough VAS in subjects with acute cough due to URTI were evaluated and the minimal important differences quantified for the first time. Cough frequency, assessed objectively with a 24-hour cough frequency monitor, was increased at baseline. Cough frequency was greater in female subjects than in males. A significant reduction in cough frequency was seen in all subjects in the second week after onset of cough. However, no clinical characteristic at baseline predicted the magnitude of change in cough frequency. There were also significant improvements in health status and cough VAS. The minimal important differences in cough frequency, LCQ and VAS in URTI were a 54%, 2.0 and 17 mm change from baseline.

The natural history of cough associated with URTI was characterised by a reduction in both cough frequency and cough bouts in most patients, as expected. There was a 41% reduction in cough frequency between visits 1 and 2 in the overall group, consistent with a rapidly changing condition. In a subgroup (27%) of patients however, cough frequency at visit 2 was either increased or unchanged from baseline, before decreasing at visit 3. This observation could have important implications when interpreting antitussive clinical trial results since any accounted mismatch in the number of subjects with early phase worsening of cough between the placebo and intervention arms could lead to misleading results. There were no

clinical characteristics at baseline such as duration of cough that prospectively identified subjects whose cough worsened. The proportion of subjects whose cough worsens during initial assessment should be reported in trials of antitussive therapy to ensure that subject groups are well matched in this respect.

Few studies have evaluated objective cough frequency in subjects with URTI. A recent study by Sunger et al investigated cough frequency over 2 consecutive days in subjects with URTI [204]. Coughs were recorded using the Vitalojak monitoring system and counted manually. They reported a similar baseline cough frequency (12.1 coughs/hour). An important difference between our studies is that I assessed cough frequency on three occasions over a 9-day period compared with Sunger et al, who took two measurements over a 2-day period. I also quantified the minimal important differences in cough frequency and other outcome parameters, allowing sample sizes to be calculated with greater confidence and facilitating clinically meaningful interpretation of results from other studies. Furthermore, longitudinal changes in cough bouts and health status were also assessed. The number of cough bouts reduced significantly between visits 1-2 but the reduction between visits 2-3 failed to reach statistical significance, in contrast to cough frequency which reduced significantly for both intervals. The relationship between health status and cough frequency and bouts was comparable.

Kuhn et al also assessed cough frequency in URTI in their study of the efficacy of the expectorant guaifenesin [271]. Duration of cough at study recruitment was earlier than in this study (2 days vs. 4 days). This is likely to explain the higher cough frequency reported at baseline by Kuhn et al; 34 coughs/hr in the placebo group. Cough frequency on the 4^{th} day from onset of cough, which would be comparable to the baseline visit in this study, was similar (16 coughs/hr). There were also important differences in the cough detection methodology. A voice-activated tape recorder was used, in contrast to continuous MP3 sound recording in this study. Subjects were confined to a study room in the study by Kuhn et al whereas in this study the LCM allowed ambulatory cough monitoring. Similarly, in the study by Pavesi et al of dextromethorphan in URTI, cough monitoring was assessed using a system that required subjects to remain in a confined environment [184].

The minimal important difference in cough frequency over a 4 day period was found to be substantial, a 54% change from baseline. Such a magnitude of change in cough frequency is noteworthy because it relates to subjects reporting only a small degree of change in their cough. This change was observed with natural recovery alone. Clinical trials of antitussive therapy, particularly those conducted over several days, should therefore aim for greater than 54% reduction in cough frequency. This may be difficult to achieve as suggested by the findings of Pavesi et al (13% reduction in cough frequency with dextromethorphan over placebo) [184]. I did not investigate the placebo effect that is often seen in cough studies [203].Further studies should explore the potential to evaluate antitussive therapy over a shorter duration, such as single dose studies, where the change in cough frequency with natural recovery is likely to be less marked. The minimal important difference in VAS in acute cough has been quantified for the first time, a 17 mm change. The VAS is a widely used, simple and valid tool for the assessment of global cough severity. This finding should facilitate clinical interpretation of VAS data in future studies. The minimal important difference in LCQ important to patients was 2.0, similar to that reported in a previous study [148].

The purpose of estimating the minimal important difference (MID) was to determine sample sizes for future studies [245]. The methodology used to for determine the MIDs was similar to that used in other studies, but some caution is advised in interpreting the MID data since the cough parameters are rapidly changing with natural recovery alone. The MIDs were determined at visit 2 because it was envisaged that cough would have resolved or be near resolution in most subjects by visit 3, which would make the assessment of the MID difficult. Further studies should assess whether the magnitude of MIDs are influenced by the time course of illness. The sample sizes required in future parallel group studies to detect the MIDs in cough frequency, LCQ and VAS were calculated based on the MID data. The sample size was greatest for LCQ. This reflects the relatively smaller MID for the LCQ compared with that for cough frequency. The sample size for cough frequency is consistent with that suggested by Sunger et al [204]. A strength of my sample size calculation is that I used an anchor-based method to determine the MID, ensuring

that the estimate is clinically relevant. Sample size calculations were also calculated using AUC data. The AUC is a measure of the trajectory of the outcome parameter over a period of time and hence already includes the effect of natural recovery in this study, unlike the baseline cough frequency rate. Therefore, the advantage of using AUC data for sample size calculations is that it will power for detection of change in addition to that due to natural recovery. The samples sizes calculated by responder analysis were larger, consistent with previous studies using responder analysis methods [272]. The limitations of responder analysis are its reduced power relative to that of continuous outcome measure scales and the arbitrary nature of the definition of a response; both are thought to increase the sample size [272]. I investigated the factors that may influence the magnitude of change in cough frequency since this affects the sample size calculation. Although the study was underpowered to study this with confidence, none of the parameters assessed predicted the change in cough frequency. Sample sizes were calculated for a parallel group study design. I would not propose a cross-over design for future studies because URTI is a rapidly changing condition and the data from this study suggests that the sample size for parallel group studies is achievable, but others have suggested that cross-over studies may be possible [204].

Potential predictors of 24-hour cough frequency at baseline were evaluated. A simple, brief screening tool that identifies patients with low 24-hour cough frequency may be useful for research studies and clinical trials to facilitate recruitment of patients with a clinically significant cough frequency. Cough frequency in the first hour was the best predictor of 24-hour cough frequency, whereas subjective assessments of cough severity were poor predictors. Cough frequency in the first hour <20.5 coughs/hour had a 91% sensitivity to identify low cough frequency. A limitation of this threshold is that approximately one third of subjects will potentially be misclassified as having a low frequency cough and therefore be excluded from studies (67% positive predictive value). Further evaluation of first-hour cough frequency as a screening tool in clinical trials is warranted. At the end of the study, 52% of subjects still had cough frequency rates above normal, suggesting that cough frequency due to URTI may take some weeks

to return to within normal limits in a significant number of subjects. This has previously been reported by Jones et al who noted that cough (assessed subjectively) persisted 2 weeks after onset in a similar proportion of subjects (58%) [202].

Health status was severely impaired in cough associated with URTI, affecting all domains of the LCQ. This is consistent with previous studies [148, 273]. The degree of health status impairment was comparable to patients with chronic cough [11]. In contrast to chronic cough, health status was only transiently impaired, returning to near normal levels by visit 3. The relationship between health status and VAS with cough frequency was best at visits 2 and 3. However, the correlation was moderate, suggesting that other factors, such as cough intensity, may be important determinants of cough severity in URTI [120, 146, 198]. The relationship between subjective and objective parameters was poor at visit 1. It is possible that symptoms such as rhinorrhea, headache, sleep disturbance and those causing disruption to daily activities had a significant impact on general health status in the early stages of the illness. The relationship between longitudinal changes in subjective and objective measures of cough was more consistent than that with cross-sectional assessments. At baseline, the relationship with cough frequency was better with the LCQ compared to VAS. However, the change in VAS was a better representative of GRCQ category, and particularly in subjects reporting a large change in cough severity. The reasons for this are unclear, and further studies with larger number of subjects are needed to investigate whether there are important differences in the performance of subjective outcome tools.

There are limitations to this study. Although the cough frequency of the overall group reduced significantly over the duration of the study, a significant proportion of subjects still had abnormally raised cough frequency at visit 3. Ideally, further assessments would have been made until the resolution of cough or until a plateau in cough frequency was observed. Additional assessments during the early phase of illness would also have been desirable. The study population was young and did not have co-morbidity, it is therefore not known if cough frequency in older subjects differs; this needs further investigation. However, in chronic cough, there is no

significant relationship between cough frequency and age [170]. The duration of cough at recruitment was not identical for all subjects; this could have had an impact on the degree of change in cough severity between study visits. The study was underpowered to perform a sub-analysis of patients with identical duration from onset of cough. The recruitment of patients with an identical duration of cough in the early phase of illness is challenging because of the unpredictable incidence and rapidly changing nature of acute cough. However, the impact of this limitation may be less marked in this study, since no association was found between the duration of cough and change in cough frequency. The viral aetiology of acute cough was not investigated in this study. It is possible that differences in the type of virus will have an impact on the severity of cough. Studies using induced viral URTIs could address this. It is also possible that non-infectious causes may have been responsible for acute cough in some subjects.

It is possible that inaccuracies in the LCM cough detection software have affected the findings since the LCM was validated in subjects with chronic cough. However, the cough recordings in the current study were ambulatory and performed in the subjects' own environment, similar to the validation studies in chronic cough [198]. Furthermore, the cough frequency rates observed in this study were similar to those in another study of acute cough in which coughs were counted manually [204]. My definition of low cough frequency was based on an arbitrary threshold of <10 coughs/hr. This was chosen this because it was less than the average cough frequency for subjects with URTI but higher than that reported for healthy subjects [274]. Further thresholds should be evaluated in larger studies. I only investigated the potential for the first hour cough frequency to predict 24-hour cough frequency and both measurements were obtained from the same recording. These limitations should be addressed by investigating longer duration recordings conducted separately from the 24-hour recording. I did not evaluate cough intensity in this study since its measurement is not currently possible in an ambulatory setting. It is possible that the MIDs differed between those who improved and those who deteriorated; the study was underpowered to assess this. Lastly, it is possible that subjects may have associated the change in cough assessed with the GRCQ more

closely with their cough severity at the follow up visit compared to baseline [275]. The short interval between study visits, 4 days, should have minimised recall bias but this should be addressed in future studies by determining change prospectively.

4.7 Conclusion

In conclusion, a number of valid tools are available to assess cough severity in acute cough secondary to URTI. 24-hour cough frequency monitoring is a practical, objective and responsive outcome parameter. Cough frequency in patients with URTI was significantly raised. The MID in 24-hour cough frequency was 54%. Health status was significantly impaired due to cough in URTI and returned to near normal levels with recovery. The relationship between cough frequency and health status was weak to moderate, suggesting that both subjective and objective outcome tools should be used to assess cough comprehensively. The findings of this study will facilitate the design of future trials of therapy. The sample sizes required for parallel group studies for a range of outcome parameters are modest and achievable.

5 Four-hour cough frequency monitoring in chronic cough

This chapter was submitted in manuscript form and accepted for publication. Reference:

Lee KK, Savani A, Matos S, Evans DH, Pavord ID, Birring SS. Four-hour cough frequency monitoring in chronic cough. Chest 2012;142(5):1237-1243

5.1 Abstract

Background: The recent development of automated cough monitors has enabled objective assessment of cough frequency. A study was undertaken to determine whether short-duration recordings (<6 hrs) accurately reflect 24-hr cough frequency and to investigate their responsiveness.

Methods: One hundred adults with chronic cough underwent 24-hr cough frequency monitoring with the Leicester Cough Monitor and completed cough visual analogue scales (VAS) and the Leicester Cough Questionnaire (LCQ). Cough recordings were analysed using customised software to derive cough frequencies from 1 to 6 hrs and 24-hr recordings. Responsiveness was assessed with repeat assessments following therapeutic trials.

Results: The median (interquartile range) 24-hr cough frequency was 11.5 (5.8-26.6) coughs/hr. Four hours was considered the shortest recording duration that represented 24-hr cough frequency (ρ=0.9, p ≤0.001). Median 4-hr cough frequency was 16.6 (7.3-36.8) coughs/hr. Both 4-hr and 24-hr cough frequency correlated moderately with cough VAS (ρ=0.49, p≤0.01 and ρ=0.44, p≤0.01) and LCQ (ρ=-0.48, p≤0.01; ρ=-0.50, p≤0.01). Four-hour cough frequency was responsive to improvements in cough severity following trials of therapy.

Conclusions: Four-hour cough frequency correlates highly with 24-hr cough frequency recordings and relates equally well with subjective measures in chronic cough. Short-duration cough monitoring could be a practical tool to validate the presence of cough and assess response to trials of therapy in the clinic setting.

5.2 Introduction

The assessment of cough severity is integral to the investigation of patients with chronic cough. The demonstration of a reduction in cough severity following a therapeutic trial is widely used to establish the aetiology [78, 276]. Cough severity can be assessed by a number of methods such as patient opinion, symptom scales, patient diaries and quality of life questionnaires [6]. The subjective nature of the assessment of cough severity has led to the development of objective tools [167, 173, 185, 186, 200]. 24-hour objective cough monitoring is regarded as the gold standard for quantifying cough frequency [277]. It is not known if shorter duration cough recordings reflect cough rates obtained from 24-hour recordings. The advantages of short duration recordings are quicker analysis times and convenience for patients.

5.3 Aims

The aim of this study was to investigate the relationship between short and 24-hour duration cough frequency recordings, determine the optimal duration for short recordings and assess their responsiveness in patients undergoing therapeutic trials.

5.4 Methods

5.4.1 Subjects

100 consecutive patients with chronic cough were recruited from a general respiratory clinic that receives greater than 80% of its referrals from primary care. All patients presented with an isolated chronic cough. Chronic cough was defined as a cough lasting greater than 8 weeks duration. The cause of cough in all patients was ascertained from case note review when investigation and treatment trials were complete. All patients were assessed using a standardised diagnostic protocol [16]. A diagnosis was established if patients had suggestive history and/or investigations and a clinical response to specific therapy. Patients with idiopathic chronic cough had negative investigations and treatment trials for asthma, upper airway cough syndrome and gastro-oesophageal reflux disease. Patients with a

recent upper respiratory tract infection in the preceding 4 weeks were excluded. All subjects gave informed consent to participate in the study. This study was approved by King's College Hospital Research Ethics Committee (ref: 07/Q0703/9).

5.4.2 Subjective cough severity assessment

Health related quality of life was assessed using the Leicester Cough Questionnaire (LCQ), a validated cough-specific health status questionnaire [11]. The LCQ is self-completed, comprises of 19 items and has 3 domains: physical, psychological and social. Domain scores range from 1-7, and total score ranges from 3-21. A higher score reflects better health status. Cough symptom severity was recorded using a 100 mm cough visual analogue scale (VAS), where 100 mm indicated most severe cough and 0 mm indicated no cough.

5.4.3 Cough frequency assessment

Cough frequency was recorded with the Leicester Cough Monitor (LCM). The LCM is a validated ambulatory, semi-automated, cough monitor that measures cough frequency and has a sensitivity and specificity of 91% and 99% respectively for detecting cough [173, 198]. The LCM has been independently validated against manually counted cough recordings [173, 174]. The LCM consists of a portable MP3 sound recorder and free-field microphone that are worn for 24 hours in the patients' own environment. Short (1-6 hours) and long (24-hour) recording cough frequencies were determined from the same recording. The sound files were uploaded onto a computer for automated analysis using customised cough detection software [173]. The software is based on a keyword spotting approach widely used in speech recognition, also known as Hidden Markov Models [171, 172]. This was followed by minimal operator input to refine cough analysis and generate a final report. Coughs were detected as single events whether occurring in isolation or clusters. Cough monitoring set-up took less than 5 minutes, automated cough detection analysis 60-90 minutes and operator refinement and report generation 10 minutes.

5.4.4 Determination of optimal short recording duration

The shortest LCM recording duration that was representative of 24-hour cough frequency (CF_{24}) was determined by assessing the relationship with CF_{24}, health status (LCQ) and cough VAS. This was done sequentially for 1 to 6-hour recordings. The optimal short recording duration was determined if (1) there was good agreement between short duration cough frequency and awake cough counts; intra-class correlation coefficient >0.8, (2) the relationship of short recordings with subjective cough outcome parameters was consistent with those of CF_{24} and (3) the short recordings were responsive; effect size >0.4. The optimal time of day for conducting short recording studies was determined by assessing the relationship between short recording cough frequency commenced at different times of day and overall daytime cough frequency (CF_{day}). Daytime and nighttime periods were established from self-reported awakening and bed times using patient diaries.

5.4.5 Protocol

Patient characteristics were recorded using a structured questionnaire during a clinic visit. Subjective cough severity and cough specific health related quality of life were recorded using the cough VAS and LCQ respectively. The LCM was attached to patients during the daytime and worn for 24 hours. Patients were encouraged to resume normal daily activity in their own environment during recordings. A subgroup of 20 patients undergoing trials of therapy (inhaled and nasal corticosteroids) underwent repeat LCM, LCQ and cough VAS assessments after 2 months. The repeat assessment was performed at the same time of day as the first recording. Response was defined as "no response", "partial response" or "good response" by asking patients to rate the improvement in their cough severity at the second visit. The relationship between cough frequency during self-reported day-time (CF_{day}) and night-time hours (CF_{night}) was compared with day-time and night-time cough frequency determined by arbitrary times ($CF_{08\text{-}22}$ and $CF_{22\text{-}08}$) to investigate the potential to do cough monitoring without using patient diaries to define day-time and night-time periods. The effect of meals (1 hour before vs. after) and awakening (first vs. second hour) on cough frequency were investigated to assess the potential for these situations to affect short duration recordings.

5.4.6 Statistical analysis

Statistical analysis was performed with SPSS version 16 and GraphPad Prism 5 software. Cough frequency is presented as 24-hour cough frequency (CF_{24}), daytime cough frequency (CF_{day}), nighttime cough frequency (CF_{night}) and as absolute cough counts. Cough frequency data was non-normally distributed and therefore Mann-Whitney tests, Kruskal-Wallis tests and Spearman's ρ correlation coefficients were used for analysis. Effect sizes were calculated as the difference in mean cough frequency / standard deviation of baseline cough frequency. Confidence intervals for effect sizes were constructed using 'R' package (R Development Core Team) [278]. Sample size calculation was limited by the exploratory nature of this study in an unselected population with unexplained chronic cough. I therefore chose to recruit a large population similar to that used in the development of other cough severity tools [11].

5.5 Results

100 patients with chronic cough were recruited. The primary causes of cough were asthma (n=24), eosinophilic bronchitis (n=7), rhinitis (n=9), gastro-oesophageal reflux disease (GORD) (n=3), idiopathic chronic cough (n=29), post-viral cough (n=7), sarcoidosis (n=6), interstitial lung disease (n=8), obstructive sleep apnoea (n=2), bronchiectasis (n=2), chronic bronchitis (n=1), ACE-inhibitor induced (n=1) and post-infective (n=1)). Baseline characteristics are shown in Table 5-1. There were no significant differences in age, lung function, quality of life or cough VAS between diagnostic groups. No patients reported adverse incidents with cough monitoring assessment.

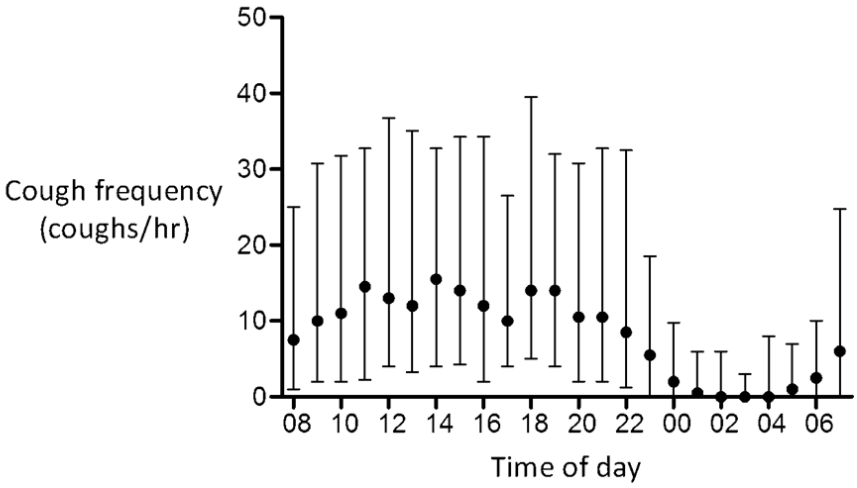
Table 5-1 Patient baseline characteristics

Characteristic		Value
Number		100
Male (%)		43
Age (years)		54 (1)
Cough duration (months)		40 (7)
FEV_1 (% predicted)		90 (2)
FVC (% predicted)		97 (3)
BMI (kg/m^2)		32 (4)
Smoking (%):	Never	80
	Ex	15
	Current	5

Data presented as mean (standard error of mean) or %. FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; BMI: body mass index.

The median (interquartile range) total cough counts during awake-hours, sleep-hours and 24-hours were 216 (124 to 606) coughs, 31 (8 to 62) coughs and 277 (139 to 637) coughs respectively. The median (IQR) 24-hour cough frequency (CF_{24}) was 11.5 (5.8 to 26.6) coughs/hour. There was no significant relationship between CF_{24} and age, gender, forced expiratory volume in 1 second (FEV_1), body mass index (BMI) or duration of cough. There was no significant difference in cough frequency before and after meals (median cough frequency 14.0 coughs/hr vs. 12.5 coughs/hr, p=0.43). There was also no significant difference in cough frequency between the first and second hour after awakening (p=0.65). Cough frequency during awake-hours was significantly greater than that during sleep; median CF_{day} 13.2 vs. CF_{night} 4.2 coughs/hr; difference between medians 8.9; 95% confidence interval of difference 6.8 to 12.6; p<0.001 (Figure 5-1). CF_{24} was more strongly related to CF_{day} (ρ=0.98, p<0.001) than CF_{night} (ρ=0.62, p<0.001). Cough frequency during the arbitrary day-time period between 0800 to 2200 and night-time period between 2200 to 0800 related well to actual CF_{day} and CF_{night} (ρ=0.99; p<0.001 and ρ=0.78; p<0.001 respectively). Cough frequency (CF_{24}) was moderately related to health related quality of life and cough VAS (Table 5-2).

Figure 5-1 Diurnal variation in cough frequency in patients with chronic cough



Data presented as median (interquartile range)

Table 5-2 Relationship between short and long duration cough recordings, cough-specific quality of life and cough VAS

Cough frequency method	CF_{24}		QOL (LCQ)	VAS
	ρ	**ICC**	***ρ***	***ρ***
CF_1	0.77	0.63	-0.31	0.34
CF_2	0.85	0.73	-0.35	0.37
CF_3	0.88	0.79	-0.41	0.37
CF_4	**0.90**	**0.82**	**-0.48**	**0.49**
CF_5	0.92	0.84	-0.48	0.49
CF_6	0.93	0.85	-0.48	0.48
CF_{24}	-	-	-0.50	0.44

Spearman's ρ and intraclass correlation coefficients. All p-values are <0.01. CF_1-CF_6: cough frequency obtained from first hour of recording to first 6 hours of recording; CF_{24}: 24-hour cough frequency; ICC: intraclass correlation coefficient; LCQ: Leicester Cough Questionnaire; QOL: quality of life; VAS: cough visual analogue scale.

There was a strong and significant correlation between all short duration cough frequency recordings and CF_{24} (Table 5-2). The relationship between subjective cough assessment scores (cough VAS and LCQ) and cough frequency determined from recordings of ≥4 hours duration was comparable to that of $CF_{24.}$ Cough frequency from 4-hour recordings (CF_4) was selected for further analysis since it was the shortest recording duration that retained this good relationship with CF_{24} and subjective cough assessment scores. CF_4 was significantly higher than CF_{24}; median cough frequency 16.6 (7.3-36.8) coughs/hr v 11.5 (5.8-26.6) coughs/hr; difference between medians 3.5 coughs/hr; 95% confidence interval of difference 1.5 to 7.4; $p<0.001$. There was good agreement between CF_4 and CF_{24} (Figure 5-2 and Table 5-2). Cough frequency obtained from 4-hour recordings was strongly related to CF_{day} regardless of the time of day they were commenced (Table 5-3). One patient with idiopathic chronic cough had an extremely high 24-hour cough count (2977 coughs). This was verified manually. The correlation between CF_4 and CF_{24} was repeated without this patient and the relationship was unchanged.

Figure 5-2 Relationship between 4-hour and 24-hour cough frequency

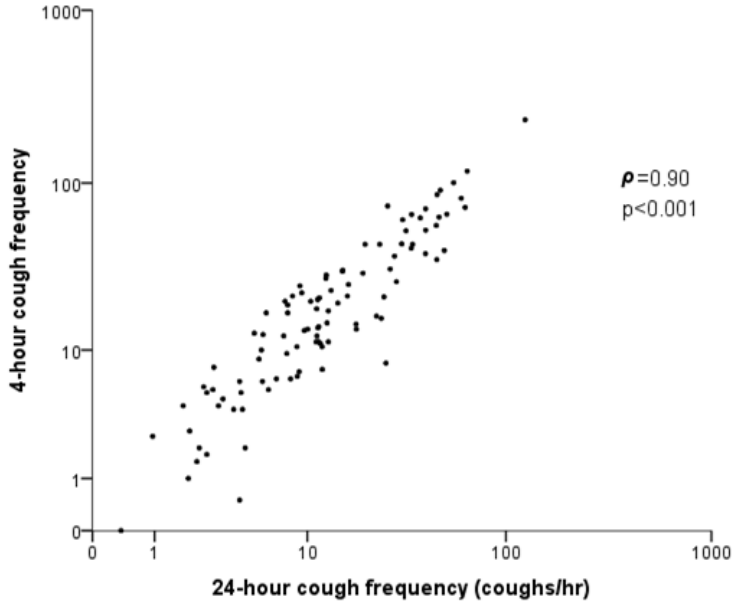


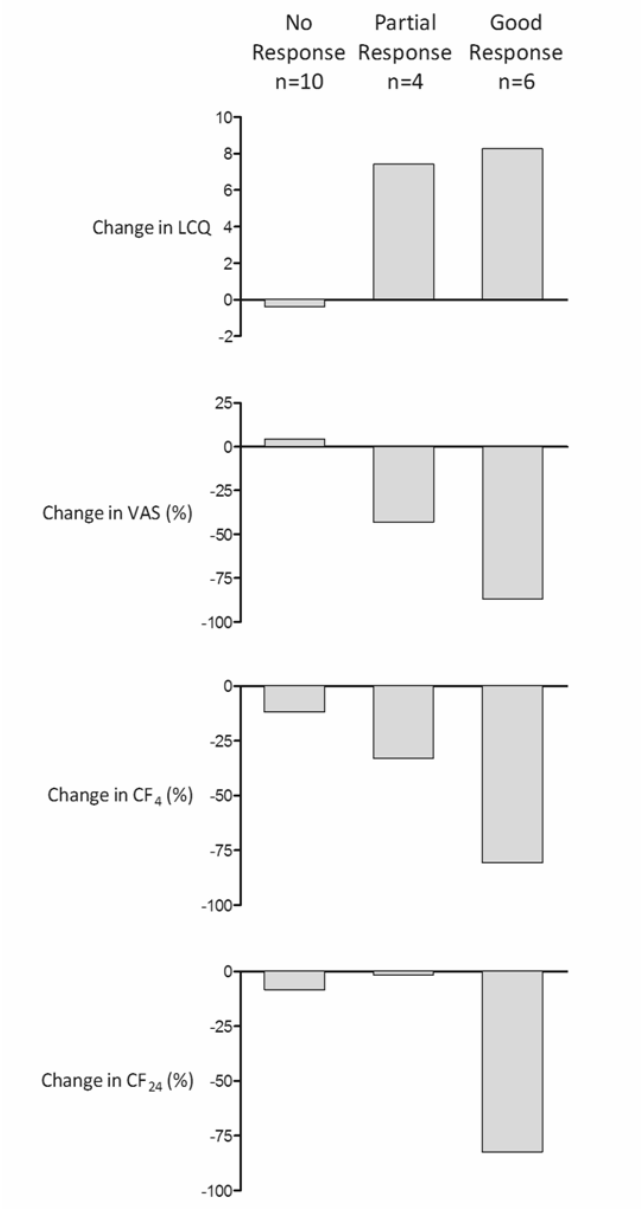
Table 5-3 Relationship between 4-hour cough frequency obtained from different times of day and awake cough frequency

4-hour recording period (time of day)	Correlation between cough frequency obtained from 4-hour and day-time recordings
8:00 AM to 12:00 PM	0.88
9:00 AM to 1:00 PM	0.88
10:00 AM to 14:00 PM	0.89
11:00 AM to 15:00 PM	0.90
12:00 PM to 16:00 PM	0.92
13:00 PM to 17:00 PM	0.94
14:00 PM to 18:00 PM	0.91
15:00 PM to 19:00 PM	0.91
16:00 PM to 20:00 PM	0.88
17:00 PM to 21:00 PM	0.88
18:00 PM to 22:00 PM	0.93

Correlation coefficients (Spearman ρ). All p-values <0.001.

In the subgroup of patients undergoing assessment of responsiveness, 6 reported a good response, 4 partial response and 10 reported no response following a trial of therapy. There were significant differences in the change in cough frequency between the 3 response categories for short recordings CF_2-CF_6 (p=0.01-0.04); for CF_1, p=0.27. CF_4 compared favourably with longer daytime recordings as an outcome measure for the assessment of response to therapeutic trials (Figure 5-3). The effect size for change in CF_4 and CF_{24} was 0.52 and 0.64 respectively (Table 5-4).

Figure 5-3 Changes in cough VAS, LCQ and cough frequency following therapeutic trials



Data presented as median percent change from baseline. LCQ: Leicester Cough Questionnaire; VAS: cough visual analogue scale; CF4: 4-hour cough frequency; CF24: 24-hour cough frequency

Table 5-4 Responsiveness of short duration cough frequency monitoring

Cough frequency recording duration	Baseline CF (coughs/hr)	Difference in CF (coughs/hr)	P-value	Effect size (95% CI)
1-hour	29.0 (6.8, 56.0)	-5.5 (-22.8, 8.3)	0.39	0.28 (-0.36 to 0.91)
2-hour	34.8 (11.8, 67.0)	-12.5 (-38.1, -3.5)	0.04	0.48 (-0.19 to 1.13)
3-hour	34.3 (10.9, 68.6)	-16.0 (-42.3, -9.3)	0.04	0.52 (-0.16 to 1.17)
4-hour	32.6 (11.3, 64.9)	-14.8 (-39.7, -5.3)	0.04	0.52 (-0.16 to 1.17)
5-hour	35.0 (12.1, 67.5)	-14.0 (-43.9, -7.1)	0.04	0.59 (-0.10 to 1.25)
6-hour	34.4 (12.4, 70.4)	-13.8 (-43.7, -8.1)	0.03	0.59 (-0.10 to 1.25
24-hour	28.5 (11.5, 44.3)	-9.0 (-25.8, 1.3)	0.07	0.64 (-0.06 to 1.31)

Responsiveness of short duration cough frequency measures in patients with chronic cough undergoing trials of therapy (inhaled or nasal corticosteroids). Data presented as median (IQR) unless otherwise indicated; CF: cough frequency; CI: confidence interval.

5.6 Discussion

This is the first study to investigate cough frequency measurement with short cough monitor recordings in patients with chronic cough. There was good agreement between 4-hour and 24-hour cough recordings. Both 4-hour and 24-hour cough frequencies were associated with subjective measures of cough severity. 4-hour recordings were responsive, suggesting they could be used to assess the efficacy of therapeutic trials.

Cough monitors are usually set to record for 24 hours. I hypothesised that short daytime recordings could reflect longer recordings since the majority of coughs occur during the day [119, 173]. The findings of this study have shown that cough counts from 4-hour recordings are strongly correlated to 24-hour recordings and have a similar relationship with subjective parameters. The time of day for starting the monitoring did not affect the performance of short duration recordings. This is most likely due to the stability of cough counts during daytime [146]. There was also no significant impact of meal times and awakening on cough frequency.

Cough frequency from 4-hour recordings was greater than that from 24-hour recordings. This was due to the low frequency of cough during nighttime in 24-hour recordings. Other investigators have also reported that nighttime cough frequencies are lower than daytime [120, 146]. A good correlation and agreement was found between 4-hour and 24-hour cough frequencies despite the impact of diurnal variation on 24-hour cough frequencies. The wide range of CF_4 suggests that this measure may be able to discriminate patients with low and high cough frequencies. Furthermore, in a small group of patients undergoing trials of therapy, CF_4 was responsive to change, suggesting it may be useful in the assessment of patients undergoing therapeutic trials.

The shortest recording reflective of 24-hour cough frequency was determined by predefined criteria - agreement with CF_{24}, association with subjective cough outcome parameters and responsiveness. Longer recordings, such as CF_6, had better agreement and responsiveness than CF_4 but this difference was considered marginal. The advantage of the considerably shorter CF_4 recording may outweigh

the minor improvements in agreement and responsiveness with longer recordings. Recordings less than 4 hours had a weaker relationship with cough severity and health related quality of life, although this may not limit the use of shorter cough recordings in the assessment of cough frequency. Cough recordings as short as CF_2 were responsive and should be evaluated further.

There was no significant relationship between cough frequency and sex, consistent with another study [72]. This may seem surprising since females are more likely to seek medical attention for cough, have a more heightened cough reflex and report a greater impairment in cough specific quality of life [48, 273, 279]. Faruqi et al and Kelsall et al however, have reported higher cough frequency in female patients with cough [146, 279]. The reason for inconsistent findings regarding the relationship between cough frequency and gender is unclear. It is possible that the lack of gender difference in cough frequency in this study may be due to differences in the performance of the cough detection software between genders; this needs further investigation. The findings of this study raise the possibility that the differences in quality of life and the need to seek medical attention may be related to factors other than cough frequency such as cough intensity or the presence of adverse cough related symptoms such as urinary incontinence. It is not known if other cough sound characteristics such as bandwidth and energy could yield diagnostic information; this needs further investigation. As reported previously, there was a moderate relationship between cough frequency and self-reported cough symptom severity and health related quality of life [120, 146, 198]. This supports the possibility that cough severity may be influenced by unaccounted factors such as cough intensity, urge to cough, personality traits and the presence of adverse symptoms related to cough [137, 280]. Little is known about cough intensity since it is difficult to measure and the gold standard has not been established. Cough sound recorders may be an alternative to physiological measurement of cough intensity and deserve further study. The lack of a strong relationship between subjective cough severity and objective measures of cough frequency suggests that a combination of assessment tools ought to be used to assess cough comprehensively

[146, 147]. The optimal combination of cough severity measures needs to be determined.

There are some limitations to this study. Short daytime cough recordings do not capture cough during sleep; this can only be done by overnight or 24-hour recordings. Longer recordings may be necessary to evaluate drugs that are metabolised slowly. Studies that use short recordings will need a larger sample size since CF_4 is more variable than CF_{24}. The agreement between CF_4 and CF_{24} was good when the whole study group was analysed but there was disagreement in some individual patients. The reason for this is unclear but the effects of diurnal variation, variable sleep duration and acclimatisation to the cough recorder during longer recordings are possible. The assessment of responsiveness of cough frequency monitoring was limited by the small number of patients studied and this may have been responsible for the wide confidence intervals for the effect sizes. Larger studies are needed to confirm the responsiveness of short and long duration recordings and the factors that influence them. The study was underpowered to detect differences in cough frequency between categories of chronic cough. The prevalence of idiopathic chronic cough was high in this study (29%), which may reflect increasing numbers of tertiary referrals but is consistent with the experience of other clinics [80]. The prevalence of GERD associated cough in the study was low. A low prevalence of GERD associated cough has also been reported by other investigators and may reflect differences in the evaluation of GERD [32, 36]. The purpose of this study however, was to evaluate sound based cough frequency assessment irrespective of diagnostic labelling. Cough severity is likely to be influenced by other factors in addition to the frequency of coughs, such as the intensity; this was not evaluated and emphasises the pressing need to develop non-invasive tools that can assess cough intensity. It is possible that inaccuracies in the LCM automated cough detection could have affected the findings of this study. The LCM, however, has been validated against manually counted cough recordings and independently by another specialist cough clinic [169, 173]. The repeatability and responsiveness of the LCM supports its clinical validity [198]. Furthermore, the LCM has been evaluated in a randomised controlled trial setting, demonstrating its

potential for the evaluation of antitussive drugs [176]. Finally, short and 24-hour cough frequencies were obtained from the same recording. It is possible that patients would have behaved differently if they underwent 4-hour rather than 24-hour monitoring. Prospective studies with 4-hour cough frequency monitoring are therefore needed to confirm the findings of this study.

5.7 Conclusion

In conclusion, this study demonstrated that objective cough frequency monitoring can be used in the clinic setting to validate the presence of cough and may be useful in assessing the response to trials of therapy. The findings suggest that shorter 4-hour recordings may be sufficient to assess cough frequency. Shorter recordings are potentially more convenient for patients, require less time for analysis and are more practical for use in clinical trials.

6 The intensity of voluntary, induced and spontaneous cough

6.1 Abstract

Rationale: The intensity or strength of cough is an important determinant of cough severity. Few studies have investigated the intensity of cough in patients with chronic cough.

Objectives: To investigate the intensity of voluntary, induced and spontaneous cough in patients with chronic cough with physiological measures.

Methods: Patients with chronic cough and healthy subjects underwent physiological assessment of the intensity of maximum voluntary, capsaicin induced and spontaneous cough. Assessments included cough gastric (P_{ga}) and oesophageal pressure (P_{oes}), peak cough flow rate (PCFR) and compression phase duration (CPD). Expiratory muscle strength (twitch gastric pressure, Twitch T_{10} P_{ga}) and activation of abdominal muscles by electromyography (EMG_{abdo}) were also assessed. Patients with cough also rated the intensity of cough using a visual analogue scale (VAS).

Results: Most spontaneous and induced coughs occurred within bouts in contrast to voluntary coughs that were all single events. P_{oes}, P_{ga} and PCFR during maximum voluntary cough was significantly greater in patients with chronic cough compared with controls when taking into account the preceding inspired volume (p=0.003 to 0.042). There was no significant difference in Twitch T_{10} P_{ga} or EMG_{abdo} between patients and controls but CPD was increased in female patients with cough compared to healthy controls (mean ± SD CPD 0.50 ± 0.22 vs. 0.28 ± 0.17 seconds; p=0.007). The mean ± SD P_{oes} during spontaneous cough was comparable to induced cough (128 ± 28 vs. 122 ± 37 cmH_2O, p=0.686) but less than maximum voluntary cough (170 ± 46 cmH_2O, p=0.020). Mean ± SD PCFR:$PEFR_{pred}$ during induced, spontaneous and maximum voluntary cough were 36, 82 and 143 respectively (ANOVA, p<0.001). Median within-subject correlation coefficients between cough intensity VAS and P_{oes}, P_{ga}, PCFR and EMG_{abdo} were ρ=0.86 to 0.9.

Conclusions: The intensity of voluntary cough is increased in patients with chronic cough compared with healthy controls. Physiological measures of cough intensity were strongly correlated with subjective perception of cough intensity in most subjects. The mechanism for the increase in cough intensity in patients is unclear; no difference in expiratory muscle strength was found between patients and controls. Further studies should evaluate the compressive phase of cough in more detail. Cough peak flow rate, pressure and gastric pressure are important and relevant measures of cough intensity in patients with chronic cough.

6.2 Introduction

Chronic cough is a common condition associated with significant physical and psychological morbidity [11]. Recent studies have reported a weak relationship between health-related quality of life and cough frequency [198]. This had led to the suggestion that cough intensity may be important in some patients [52, 137]. Few studies have investigated the intensity of cough and, in particular, there is a paucity of studies that have assessed it objectively.

6.3 Aims

The aim of this study was to investigate the physiological characteristics and intensity of voluntary, induced (reflex) and spontaneous cough in patients with chronic cough and healthy subjects.

6.4 Methods

6.4.1 Subjects

Consecutive patients referred for investigation of a chronic cough were recruited from a respiratory outpatient clinic. All had cough for greater than 8 weeks and were symptomatic at the time of recruitment. The cause of cough was established following investigation and trials of treatment according to a standardised protocol [36]. Exclusion criteria were upper respiratory tract infection within the past 4 weeks, current smokers or history of smoking within the past 1 year, history of neuromuscular disorders and connective tissue disease. Healthy control volunteers

were recruited through local advertising. Exclusion criteria in addition to those listed above were a history of respiratory disease and abnormal lung function (FEV_1:FVC <80%). All subjects gave informed consent and the study had received ethical approval (East London and the City Research Ethics Committee 10/H0703/6)

6.4.2 Physiological measures

6.4.2.1 Cough oesophageal and gastric pressure

Oesophageal pressure (P_{oes}) and gastric pressure (P_{ga}) were measured in accordance with American Thoracic Society/ European Respiratory Society recommendations [231]. Balloon catheters (Cooper Surgical, Berlin, Germany) were inserted nasally, attached to individual pressure transducers (MP45; Validyne, Northridge, CA, USA) and amplified (CD-280 amplifier; Validyne). Cough P_{oes} was defined as the maximum pressure during coughs and P_{ga} the trough-to-peak pressure during coughs (Figure 1).

6.4.2.2 Cough flow rate and inspiratory volume

Respiratory flow was measured at the mouth using a Fleisch type pneumotachograph (P.K. Morgan Ltd, Kent, UK) attached to a full-face mask (Hans Rudolph Inc, Kansas City, USA). The pneumotachograph was calibrated prior to each study by 2-point calibration using a rotameter. Peak cough flow rate (PCFR), the maximum expiratory flow achieved during cough, was recorded and expressed as a percentage of predicted peak expiratory flow rate ($PEFR_{pred}$), to correct for age, sex and height. Inspiratory volume (IV) and cough compressive phase duration (CPD) were calculated from the respiratory flow signal during coughs. On-screen cursors were placed automatically by a customised software script to ensure standardisation. The accuracy of all cursor positions were verified manually prior to calculation.

6.4.2.3 Abdominal electromyography (EMG_{abdo}) measurement

EMG was recorded from the right rectus abdominis muscle using 55 mm diameter Ag-AgCl electrodes (Kendall liquid gel electrodes, Tyco healthcare, Hampshire, UK).

Prior to electrode attachment, the skin was thoroughly prepared using an abrasion gel (Nuprep abrasive skin gel, Weaver & Co, USA) [229]. The active electrode was placed 5 cm from the midline, just below the level of the umbilicus, and the reference electrode placed 5 cm laterally [133]. The earth electrode was placed over the anterior superior iliac spine. EMG signals were amplified and digitally filtered between 10 Hz and 2,000 Hz (1902 signal conditioner, Cambridge Electronic Design, Cambridge, UK). Peak abdominal EMG activity (EMG_{abdo}) was taken as the absolute peak of the root-mean-squared EMG trace (50 ms windows) for any given cough [211, 214]. For group analyses, EMG data was normalised by expressing EMG_{abdo} for each cough as a fraction of the largest EMG_{abdo} observed during maximum voluntary cough and following non-volitional lower thoracic nerve root magnetic stimulation at 100% stimulator output (see below) [220].

6.4.3 Respiratory Muscle Strength

Non-volitional assessment of expiratory (abdominal) muscle strength was assessed by measuring gastric pressure during lower thoracic nerve root magnetic stimulations (twitch gastric pressure, Twitch T_{10} P_{ga}) [111, 226, 255]. Stimulations were delivered using a double energy stimulator (Magstim Co Ltd, Dyfed, Wales) at maximum output and a 90 mm circular coil. Twitch T_{10} P_{ga} was determined from the average response to five stimulations. In order to minimise potentiation, subjects were rested for 20 minutes prior to magnetic stimulation whilst refraining from talking or coughing [217]. All stimulations were performed with the subject relaxed and at end-expiration [111]. The optimal coil position for delivering stimulations was defined as the position at which the largest P_{ga} response was evoked following stimulations at the 9^{th}, 10^{th} and 11^{th} thoracic vertebrae [258]. Supramaximality of the magnetic stimulation was assessed by delivering stimulations of different power and demonstrating a plateau effect in the evoked abdominal compound muscle action potential (CMAP) amplitude with increasing magnetic power (see section 3.8.2) [217, 259]. Supramaximality was defined as the absence of a significant difference in mean CMAP between 100% and 90% stimulator output [217, 259]

6.4.4 Lung function

Spirometry and peak expiratory flow rate were measured in accordance with international guidelines [242, 243].

6.4.5 Protocol

All subjects participated in voluntary and induced cough studies. A subgroup of 9 consecutive patients with chronic cough also underwent study of spontaneous cough. P_{oes}, P_{ga}, EMG_{abdo} and flow were measured during each study.

6.4.5.1 Spontaneous Cough

Patients with cough were monitored continuously for a minimum of 10 minutes or until >10 coughs were recorded. Subjects were asked not to suppress cough but to cough freely if the urge arose.

6.4.5.2 Maximum Voluntary Cough

Maximum voluntary cough (MVC) was studied before induced cough to avoid any effect of capsaicin. Subjects were asked to perform >10 maximum coughs until cough P_{oes} reached a plateau and was repeatable. Sufficient time was allowed between cough events to avoid fatigue and to ensure the return of lung volume to functional residual capacity before the subsequent effort. The MVC was the largest value observed during the protocol.

6.4.5.3 Induced cough

Reflex cough was evoked using nebulised sterile solutions of capsaicin (Sigma-Aldrich, Missouri, USA) delivered via a side port into the connecting tubing of the face mask (ultrasonic nebuliser, Devilbiss Healthcare, UK). Nebulisation was undertaken for 1 minute each with saline control, followed by doubling concentrations of capsaicin (0.49-1000 µM) until subjects coughed 5 times or more (C_5). A final nebulisation of capsaicin, one doubling concentration greater than C_5 was administered. There was a 1 minute interval between nebulisations. Nebulised saline was randomly interspersed during the protocol to minimise anticipation of dosing by subjects. Subjects were asked to avoid cough suppression. An additional

concentration of capsaicin, greater than that causing 5 coughs (supra-C_5), was administered to ensure subjects were close to their maximum induced cough response. Superior repeatability has been demonstrated with supra-threshold stimuli in the assessment of the cough frequency response [215].

6.4.6 Subjective assessment of cough intensity during voluntary cough

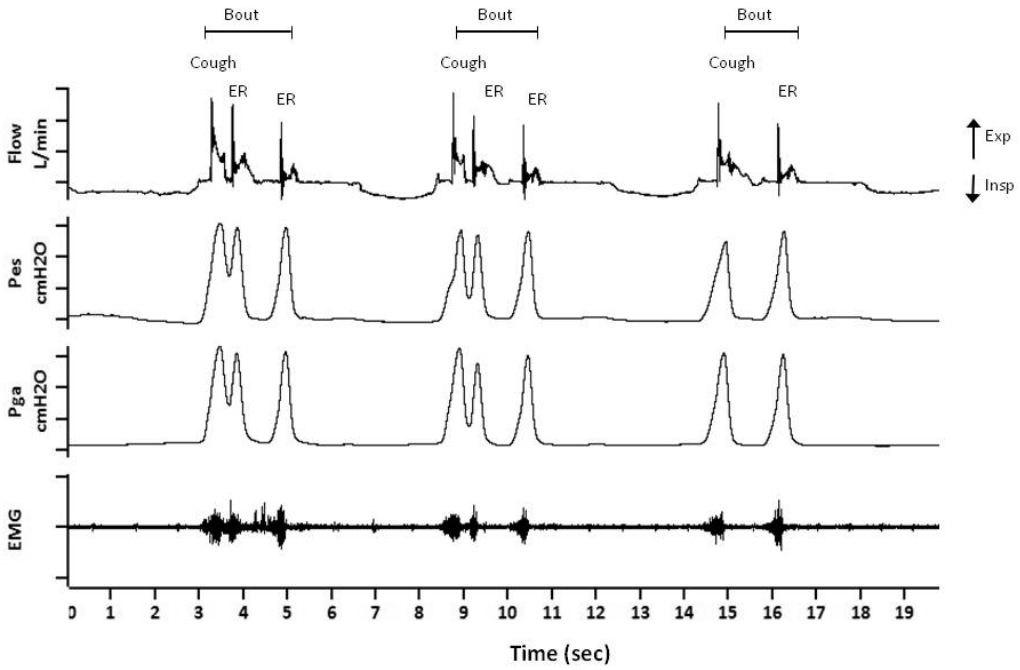
To investigate the relationship between subjective perception and physiological measures of cough intensity, a randomly selected subgroup of 8 patients with chronic cough were asked to rate the intensity of 10 voluntary coughs on 0-100 mm visual analogue scales (VAS), whilst P_{oes}, P_{ga}, PCFR and EMG_{abdo} were recorded for each cough. Subjects were asked to cough at different intensities of their choice and were blinded to the physiological measures of each cough.

6.4.7 Analysis

SPSS version 19 (IBM) and Prism version 5 (GraphPad) were used for statistical analysis. Appropriate parametric or non-parametric tests were used depending on distribution of data. Cough bouts were defined as continuous periods of coughing where individual events were <2 seconds apart (Figure 6-1) [281]. Cough events were categorised into cough (immediately preceded by inspiration) or expiratory reflex (with no preceding inspiration; ER) following interrogation of the flow signal. Although cough and ER sound similar, they differ in physiological characteristics [107]. Previous studies have reported an association between lung volume and intensity of cough [125, 218]. Therefore, P_{oes}, P_{ga}, PCFR and EMG_{abdo} were adjusted for inspired volume (IV) preceding each cough.

All physiological data were sampled at a frequency of 5,000 Hz, time synchronised, converted from analogue to digital format (Micro 1401 mk II; Cambridge Electronic Design, Cambridge, UK) and analysed on a computer with Spike 2 version 6 software (Cambridge Electronic Design, Cambridge, UK).

Figure 6-1 The physiology of capsaicin induced cough



Trace showing a number of expulsive events during capsaicin challenge testing (capsaicin concentration 1.95 µM) in a healthy male subject. P_{oes}: oesophageal pressure; P_{ga}: gastric pressure: EMG: abdominal electromyographic activity; bout: series of expulsive events with <2 second intervals between events; cough: expulsive event with preceding inspiration; ER: expiratory reflex (expulsive event without preceding inspiration); Exp: expiration; Insp: inspiration.

6.5 Results

6.5.1 Subject characteristics

28 patients with cough and 21 healthy controls were recruited. Baseline characteristics are shown in Table 6-1. The groups were matched for age, gender and lung function. The principle causes of cough in patients were: asthma (21%), gastro-oesophageal reflux disease (14%), rhinitis (4%), idiopathic (43%), post-infectious (7%), eosinophilic bronchitis (4%), obstructive sleep apnoea (4%) and bronchiectasis (4%). 21% of patients had multiple causes of cough.

Table 6-1 Baseline characteristics

	Females			Males		
	Cough (n=17)	Controls (n=10)	P-value	Cough (n=11)	Controls (n=11)	P-value
Age (years)	57 ± 14	54 ± 19	0.632	57 ± 18	50 ± 23	0.385
BMI (kg/m^2)	28.5± 7.2	23.8 ± 1.2	0.051	27.6 ± 4.3	25.8 ± 3	0.287
FEV_1 (% predicted)	100 ± 20	106 ± 22	0.452	94 ± 16	101 ± 15	0.280
FVC (% predicted)	113 ± 19	117 ± 26	0.684	97 ± 21	107 ± 19	0.269
FEV_1/FVC (%)	75 ± 9	78 ± 6	0.352	77 ± 6	76 ± 8	0.939
Cough duration (months)	36 (26-83)	-	-	50 (20-85)	-	-
LCQ score	11.2 (7.8-14.4)	20.9 (20.5-21.0)	<0.001	13.4 (10.1-16.4)	21.0 (20.8-21.0)	<0.001

Data presented as mean ± standard deviation or median (interquartile range). BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; LCQ: Leicester Cough Questionnaire (range 3-21; higher score reflects better health status).

6.5.2 Cough characteristics

In patients with chronic cough and in controls, all maximum voluntary coughs (MVC) were single events; no bouts were observed during voluntary coughs. All cough events were preceded by inspiration; there were no expiratory reflexes (ER). In contrast to MVC, most events during capsaicin induced cough and spontaneous cough occurred within bouts, and most of these events were ERs (Table 6-2). The very first event during capsaicin induced cough challenges in patients with chronic cough was an ER in 63% of challenges (Table 6-3). In contrast, an ER was the first event in 27% of spontaneous cough bouts (Table 6-3). There was no significant difference in the prevalence of first event ER between gender ($p=0.78$ and 1.00 for C_5 and supra-C_5 respectively) and cough vs. control groups ($p=0.12$ and 0.69 for C_5 and supra-C_5 respectively).

Table 6-2 The characteristics of induced and spontaneous cough

	Females		Males	
	Cough	Controls	Cough	Controls
Induced cough (C_5)				
Number of events	18 (8-26)	9 (6-16)	16 (10-28)	8 (6-10)
Events occurring in bouts (%)	100 (86-100)	100 (88-100)	100 (100-100)	100 (89-100)
ER (% of all events)	69 (57-75)	73 (67-82)	75 (60-79)	71 (63-80)
Induced cough (supra-C_5)				
Number of events	15 (13-25)	16 (10-21)	15 (8-25)	16 (10-26)
Events occurring in bouts (%)	100 (94-100)	98 (88-100)	100 (94-100)	100 (100-100)
ER (% of all events)	69 (59-78)	78 (67-85)	75 (71-79)	70 (63-80)
Spontaneous cough				
Number of events	45 (29-137)	-	19 (13-84)	-
Events occurring in bouts (%)	96 (92-100)	-	91 (81-100)	-
ER (% of all events)	62 (46-69)	-	74 (37-81)	-

Data presented as mean ± standard deviation or median (interquartile range). Cough events were categorised as those preceded by inspiration and those without inspiration (expiratory reflex, ER). A bout is a series of 2 or more consecutive events, each separated by <2 seconds. Spontaneous cough was assessed for average 30 minutes. C_5: concentration capsaicin causing ≥ 5 cough events. Supra-C_5: concentration of capsaicin one doubling dose higher than C_5.

Table 6-3 A comparison of the intensity of voluntary, induced and spontaneous cough in patients with chronic cough

	MVC	IC	SC	P-value		
				MVC vs. IC	MVC vs. SC	IC vs. SC
P_{oes} (cmH_2O)	170±46	122±37	128±28	0.250	0.020*	0.686
P_{ga} (cmH_2O)	207±60	140±76	141±43	0.156	0.030*	0.938
$PCFR:PEFR_{pred}$	143±38	36±15	82±32	<0.001*	<0.001*	0.007*
EMG_{abdo}	0.11±0.11	0.06±0.04	0.07±0.07	0.078	0.008*	0.641
ER (% of events)	0	63	27			

*Subjects are subgroup of patients with chronic cough who underwent study of spontaneous cough. Data presented as mean ± standard deviation or %. MVC: Maximum voluntary cough, IC: Induced cough - first cough or ER evoked by supra-C_5 capsaicin concentration, SC: first spontaneous cough or expiratory reflex in a bout; Poes: oesophageal pressure, P_{ga}: gastric pressure; $PCFR:PEFR_{pred}$: peak cough flow rate normalised to predicted peak expiratory flow rate; EMG_{abdo}: abdominal electromyographic activity; *: p<0.05.*

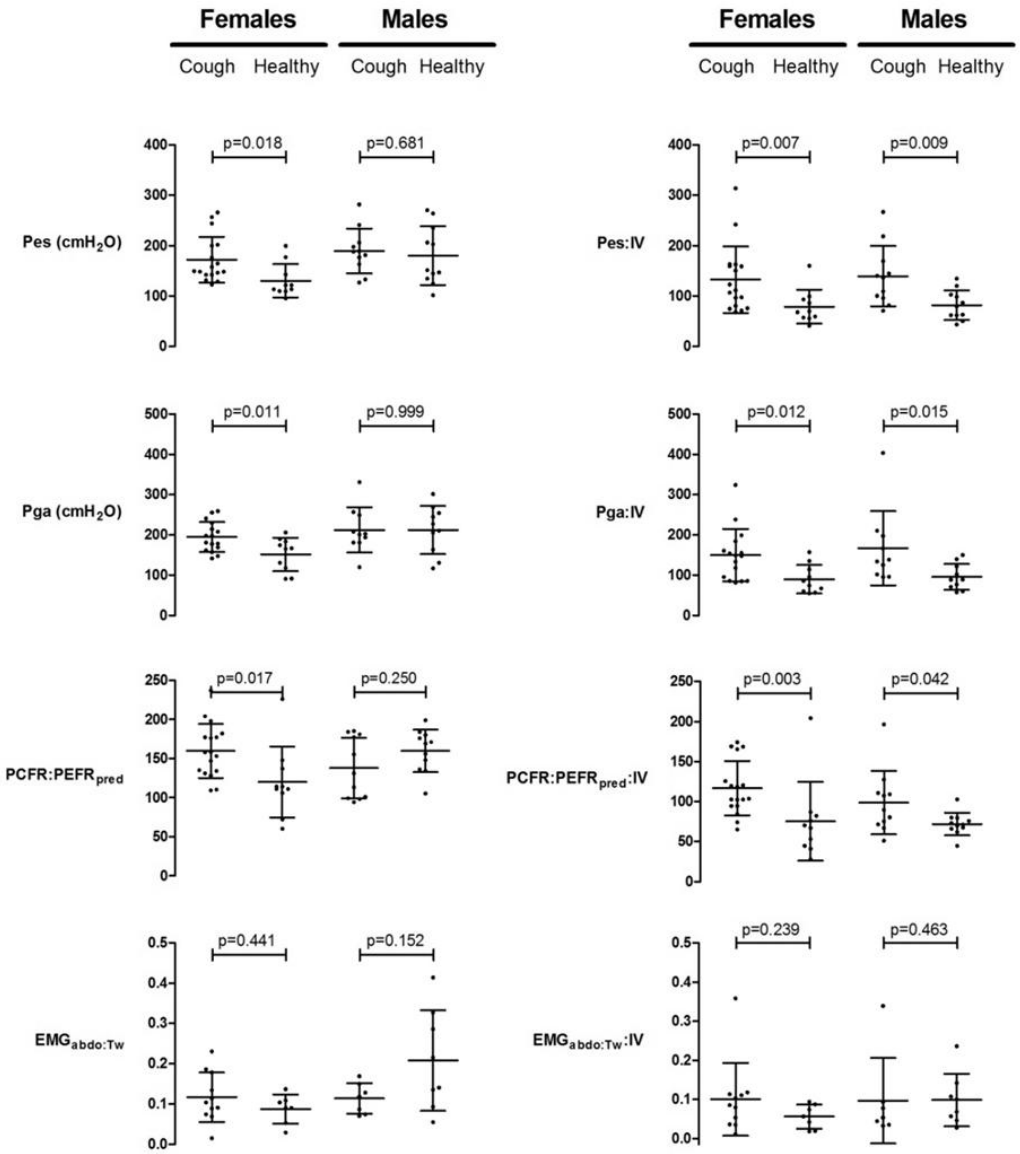
6.5.3 Cough intensity during maximum voluntary cough

During maximum voluntary cough, P_{oes}, P_{ga} and $PCFR:PEFR_{pred}$ were significantly greater in female patients compared to female controls (Figure 6-2 and Table 6-4). There was no significant difference in EMG_{abdo}. There were no differences in any cough intensity measure between male patients and controls. However, male patients with cough took lower inspired volumes of air prior to coughing (Table 6-4). When adjusted for inspired volume, P_{oes}, P_{ga} and $PCFR:PEFR_{pred}$ were significantly greater in patients with cough compared to controls for both females and males (Table 6-4).

There was no significant difference in expiratory muscle strength as assessed by Twitch T_{10} P_{ga} between patients and controls (Table 6-5). Abdominal muscle compound muscle action potential (CMAP) amplitude during twitch magnetic stimulation at maximum power was similar between patients and controls (Table 6-5). Maximal stimulation was confirmed by demonstration of a plateau in evoked

CMAP amplitude with increasing magnetic stimulator power output (Figure 6-3 and Appendix 7).

Figure 6-2 The intensity of maximum voluntary cough



Graphs on left show unadjusted values and graphs on right show values adjusted for inspired volume. Data presented as mean ± standard deviation. P_{oes}: oesophageal pressure; P_{ga}: gastric pressure; $PCFR:PEFR_{pred}$: peak cough flow rate normalised to predicted peak expiratory flow rate; $EMG_{abdo:Tw}$: abdominal electromyographic activity normalised to EMG_{abdo} during twitch magnetic stimulation; IV: inspired volume of air prior to cough.

Table 6-4 The intensity of maximum voluntary cough

	Females			Males		
	Cough (n=17)	Controls (n=10)	P-value	Cough (n=11)	Controls (n=11)	P-value
P_{oes} (cmH_2O)	172 ± 46	130 ± 33	0.018*	189 ± 44	180 ± 58	0.681
P_{ga} (cmH_2O)	195 ± 37	152 ± 41	0.011*	212 ± 56	212 ± 60	0.999
PCFR (L/min)	584±129	451±151	0.022*	713±241	853±184	0.139
PCFR:$PEFR_{pred}$	161 ± 35	120 ± 47	0.017*	138 ± 40	161 ± 26	0.250
$EMG_{abdo:Tw}$	0.12 ± 0.02	0.09 ± 0.01	0.441	0.11 ± 0.01	0.21 ± 0.04	0.152
Inspired volume (L)	1.46 ± 0.44	1.78 ±0.49	0.093	1.62 ± 0.84	2.23 ± 0.60	0.030*
Adjusted for IV						
P_{oes} /IV	133 ± 66	79 ± 34	0.007*	139 ± 60	82 ± 29	0.009*
P_{ga}/IV	150 ± 65	90 ± 35	0.012*	167 ± 92	96 ± 32	0.015*
PCFR:$PEFR_{pred}$/IV	117 ± 34	75 ± 49	0.003*	99 ± 40	72 ± 14	0.042*
$EMG_{abdo:Tw}$/IV	0.10 ± 0.09	0.06 ± 0.03	0.239	0.10 ± 0.11	0.10 ± 0.07	0.463

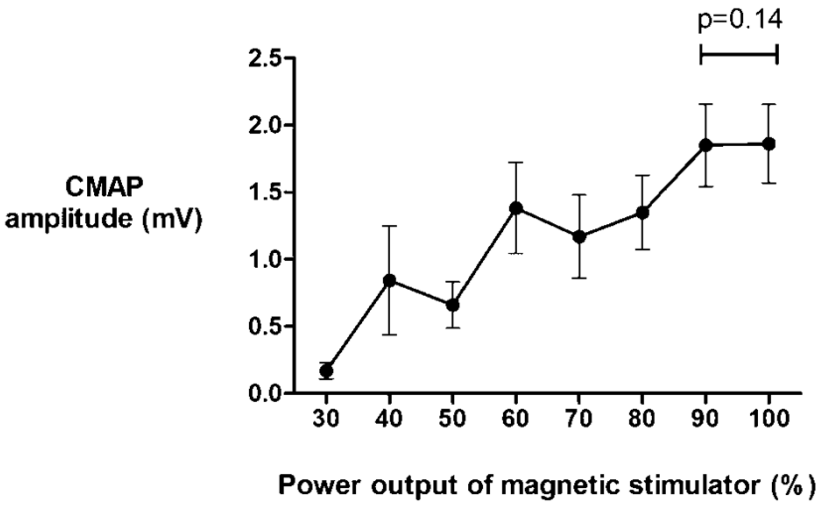
*Data presented as mean ± standard deviation. Maximum voluntary cough from 10 attempts. P_{oes}: oesophageal pressure; Pga: gastric pressure; PCFR: peak cough flow rate; PCFR:$PEFR_{pred}$ peak cough flow rate normalised to predicted peak expiratory flow rate; $EMG_{abdo:Tw}$: abdominal electromyographic activity normalised to EMG_{abdo} during twitch magnetic stimulation; IV: inspired volume of air prior to cough; *: $p<0.05$.*

Table 6-5 Respiratory muscle strength testing

	Females			Males		
	Cough	Controls	P-value	Cough	Controls	P-value
Twitch T_{10} P_{ga} (cmH_2O)	21.9 (13.2-30.3)	23.0 (15.6-37.3)	0.36	28.5 (20.1-67.0)	21.6 (19.3-63.0)	0.75
CMAP (mV)	1.10 ± 0.74	1.58 ± 1.22	0.65	2.60 ± 1.69	2.52 ± 2.55	0.54

Data presented as median (IQR) or mean ± SD. Twitch T_{10} P_{ga}: twitch gastric pressure; CMAP: abdominal compound muscle action potential.

Figure 6-3 Abdominal compound muscle action potential during magnetic stimulation



Data presented as mean ± SEM abdominal compound muscle action potential (CMAP) amplitude. A plateau of the CMAP amplitude is seen with increasing magnetic stimulator power, with maximal stimulation being achieved at 90% of power output. Data provided in Appendix 7.

Compressive phase duration (CPD) was significantly higher in female patients with cough compared to controls; mean ± SD CPD 0.50 ± 0.22 vs. 0.28 ± 0.17 seconds; mean difference 0.21 seconds; 95% CI of difference 0.05 to 0.36; p=0.007. There was no significant difference in CPD between male patients with cough and controls; mean ± SD CPD 0.35 ± 0.27 vs. 0.31 ± 0.18 seconds; p=1.00. BMI was not related to P_{oes}, P_{ga}, $EMG_{abdo:Tw}$ or PCFR; p=0.20 to 0.90.

6.5.4 Cough intensity during capsaicin Induced cough

To standardise induced coughs, only the first evoked event following inhalation of capsaicin and only subjects with a first event preceded by inspiration were included in this analysis (patients with cough n=10, controls n=11). Subjects were not subdivided by gender due to small numbers. P_{oes}, P_{ga}, and $PCFR:PEFR_{pred}$ were numerically greater in patients with cough compared to controls, but this did not reach statistical significance (Table 6-6). Taking account for inspired volume, there was a trend towards significance for greater P_{oes}, P_{ga}, and $PCFR:PEFR_{pred}$ in patients

with cough compared to controls (p=0.082, 0.054 and 0.084 respectively and p=0.282 for $EMG_{abdo:Tw}$). In induced cough, CPD did not differ between groups (p=0.76).

Table 6-6 The intensity of capsaicin induced cough

	Cough (n=10)	**Controls** (n=11)	**P-value**
P_{oes} (cm H_2o)	136 ± 64	111 ± 43	0.312
P_{ga} (cm H_2o)	143 ± 77	109 ± 39	0.224
$PCFR:PEFR_{pred}$	47 ± 19	36 ± 5	0.099
$EMG_{abdo:Tw}$	0.07 ± 0.04	0.08 ± 0.06	0.955

Data presented as mean ± standard deviation. Data is for first evoked cough event (preceded by inspiration) following inhalation of capsaicin at supra-C_5 concentration (one doubling concentration higher than that causing >5 coughs). Subjects were excluded from this analysis if their first event was an expiratory reflex. P_{oes}: oesophageal pressure, P_{ga}: gastric pressure, $PCFR:PEFR_{pred}$: peak cough flow rate normalised to predicted peak expiratory flow rate; $EMG_{abdo:Tw}$: abdominal electromyography normalised to EMG_{abdo} during twitch magnetic stimulation.

6.5.5 Cough intensity during spontaneous cough

Baseline characteristics of the subgroup of patients undergoing spontaneous cough study are presented in Table 6-7. To standardise the analysis of spontaneous cough, single events and the first event of each bout were analysed. Due to small numbers, sub-analyses for gender or different cough types were not performed. All physiological measures of spontaneous cough were significantly lower (57-75%) than those of MVC, Table 2. $PCFR:PEFR_{pred}$ was significantly greater in spontaneous cough compared to induced cough, but P_{oes}, P_{ga}, and $EMG_{abdo:Tw}$ were comparable (Table 6-3). A greater number of induced cough events were ERs compared to spontaneous and MVC (Table 6-3). In spontaneous cough, mean ± SD $PCFR:PEFR_{pred}$ was significantly greater in coughs preceded by inspiration compared to ER; 94 ± 37 vs. 48 ± 25; mean difference 51, 95% CI of difference 16 to 85; p=0.010.

Table 6-7 Spontaneous cough subgroup baseline characteristics

Characteristic	Value
Age (years)	60 ± 13
Male: Female	4:5
BMI (kg/m^2)	28.3 ± 5.5
FEV_1 (% predicted)	92 ± 24
FVC (% predicted)	100 ± 27
FEV_1/FVC (%)	76 ± 10

Data presented as mean ± SD or n. BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; LCQ: Leicester Cough Questionnaire (range 3-21; higher score reflects better health status).

6.5.6 Intensity of expiratory reflexes during spontaneous cough

P_{oes}, P_{ga} and PCFR:$PEFR_{pred}$ were greater for coughs preceded by an inspiration than for expiratory reflexes during spontaneous cough (Table 6-8). The differences in P_{oes} and cough flow were significant between female patients and healthy controls and there was a trend to significance for P_{ga}. The differences in cough intensity between male patients and controls failed to reach statistical significance (Table 6-8).

Table 6-8 Intensity of expiratory reflexes and coughs during spontaneous cough

	All subjects			Females			Males		
	Cough	ER	p-value	Cough	ER	p-value	Cough	ER	p-value
P_{oes}	148 ± 45	94 ± 27	<0.01*	141 ± 17	99 ± 20	0.02*	156 ± 69	94 ± 27	0.11
P_{ga}	169 ± 63	90 ± 34	<0.01*	164 ± 54	97 ± 27	0.06	174 ± 79	81 ± 47	0.23
PCFR	411 ± 136	182 ± 87	<0.01*	455 ± 86	218 ± 63	<0.01*	356 ± 179	182 ± 87	0.06
PCFR:$PEFR_{pred}$	102 ± 38	48 ± 25	<0.01*	126 ± 23	61 ± 18	<0.01*	73 ± 32	5 ± 25	0.06

*Data presented as mean ± SD. Comparisons made between coughs and expiratory reflexes that occurred as single events or as the first event of bouts. Mann-Whitney tests or t-tests, depending on distribution of data. P_{oes}: oesophageal pressure; P_{ga}: gastric pressure; PCFR: peak cough flow rate; $PEFR_{pred}$: predicted peak flow rate; *: p<0.05.*

6.5.7 Subjective assessment of cough intensity

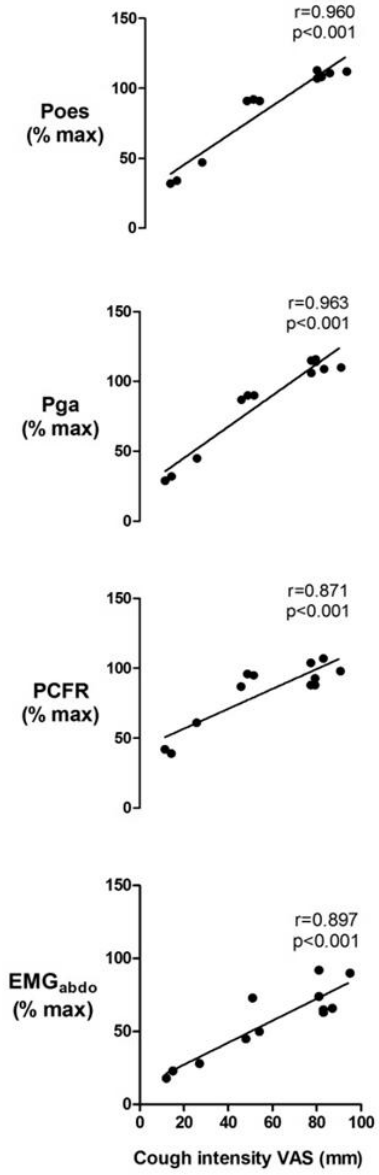
There was an association between subjective ratings of intensity of voluntary cough and physiological measures within subjects (Table 6-9). The median correlation coefficients (r) were: P_{oes} 0.84, P_{ga} 0.86, PCFR 0.82 and EMG_{abdo} 0.69 (all % of maximum measurement obtained for MVC). The relationship between subjective and objective assessments of cough intensity in a single patient is shown in Figure 6-4.

Table 6-9 The relationship between subjective rating and physiological measures of cough intensity during voluntary cough

Subject	P_{oes}	P_{ga}	PCFR	EMG_{abdo}
1	0.72††	0.75††	0.41	0.62
2	0.77†	0.86†	0.73††	0.62
3	0.90*	-	0.77†	0.90*
4	0.59	0.70††	0.62	0.53
5	0.96*	0.95*	0.96*	-
6	0.96*	0.96*	0.87*	0.90*
7	0.70*	0.85*	0.58	0.70*
8	0.94*	0.92*	0.88*	0.83†
Median	0.84	0.86	0.82	0.69

*Data presented as Spearman correlation coefficients between cough visual analogue score and objective measures of cough intensity. * p<0.001; † p=0.001 to 0.01; †† p=0.01 to 0.05. P_{oes}: oesophageal pressure; P_{ga}: gastric pressure; PCFR: peak cough flow rate; EMG_{abdo}: abdominal electromyographic activity. Subjects 3 and 5 have no data for P_{ga} and EMG_{abdo} due to technical failure of equipment.*

Figure 6-4 An example of the relationship between subjective and objective assessments of cough intensity in a patient with chronic cough



Graphs showing relationship between cough intensity visual analogue score and physiological cough intensity measures during voluntary cough in a patient with chronic cough. Spearman correlation coefficients. VAS: visual analogue scale; P_{oes}: oesophageal pressure; P_{ga}: gastric pressure; PCFR: peak cough flow rate; EMG_{abdo}: abdominal electromyographic activity.

6.6 Discussion

Few studies have investigated the physiological characteristics of cough in patients with chronic cough. This study has shown that most induced and spontaneous efforts occur within bouts. The most common sequence within a bout was a cough effort followed by ERs. ER however occurred more frequently as the very first effort during induced cough than during spontaneous cough. For both females and males with cough, maximum voluntary cough intensity was greater than that in healthy controls when adjusted for inspired volume. There was no difference in activation of abdominal muscles as measured by EMG_{abdo} or the contractile response to lower thoracic nerve root magnetic stimulation as measured by Twitch T_{10} P_{ga} between patients and controls. The compressive phase duration was greater in female patients compared to healthy controls, although this difference was not seen in males. There was a strong correlation between subjective assessment of cough intensity and objective physiological measures of cough intensity.

Expulsive efforts were categorised as cough or ER based on the presence or absence of an inspiratory phase preceding the expulsive phase. Spontaneous cough consisted largely of bouts which contained cough efforts followed by ERs. This was also true for induced cough with the exception of the very first effort of the first bout, where the proportion of ERs compared to coughs were greater than that of the first effort of the spontaneous bouts. The ER is thought to be a distinct airway reflex [123, 127]. The lack of a preceding inspiratory effort may be advantageous in some circumstances to avoid aspiration of laryngeal contents. Physiological cough intensity measures of ERs were significantly lower than those of cough efforts preceded by an inspiration. The differences between male patients and controls did not reach statistical significance but this is likely due to the small numbers studied. Cough flow and volume is dependent on the starting lung volume [125]. Since ERs occur without a preceding inspiration, they are more likely to occur at lower lung volume, and this may explain why the flow rate was significantly lower in induced compared to spontaneous cough [107]. It is important to note that there is a lack of consensus on the importance of the distinction between coughs and ERs. Whilst the lack of a preparatory inspiration in the ER represents a clear physiological

difference, the characteristic sound associated with the expulsive phase for both is similar and some investigators argue that both reflexes should be regarded equally as a cough [282]. Further evaluation of the clinical importance of the ER is needed. However, the potential differences between cough and ER should be accounted for in future studies of cough intensity.

Cough intensity was significantly greater in patients with chronic cough compared with healthy controls. Cough intensity measures were adjusted for inspired volume, since this has previously been shown to be an important determinant of peak cough flow [125]. The control group voluntary cough intensity data in this study was comparable to that reported by other investigators, suggesting that the differences observed were due to increased cough intensity in patients with cough [207, 283]. Our data suggests patients with cough have an enhanced ability to generate thoracic and abdominal pressure and flow for any given inspired volume. The increase in cough intensity was not due to increased activation of abdominal muscles as measured by EMG_{abdo}, or contractility as measured by Twitch T_{10} P_{ga}. Other investigators have also reported an enhanced cough without evidence of an increase in muscle strength [284]. It is possible that cough pressures were increased by an improved coordination of the cough manoeuvre. The findings of this study raise the possibility that, in female subjects, the increased cough intensity may have been due to an increase in the compressive phase duration. The compressive phase consists of rising thoracic pressure against a closed glottis. A longer glottis closure time may allow more time for thoracic pressure to rise closer to its maximum. It is not clear why the compressive phase duration was increased in female patients, but one hypothesis would be a learning effect. Methodological limitations need careful consideration since glottis closure was assessed indirectly and furthermore, an increase in compressive phase duration was not seen in male subjects. Future studies should include assessments of laryngeal movement and function. Another possibility for the increase in voluntary cough intensity is that, in patients with cough, muscles other than those assessed by twitch T10 magnetic stimulation are activated. In capsaicin induced cough, pressures and flow were numerically greater

in patients with cough compared with healthy controls, but the differences did not reach statistical significance and larger studies are needed.

Few studies have investigated the physiology of spontaneous cough in patients with chronic cough. Spontaneous cough intensity was shown to be between 57-75% of that seen in MVC. This is not surprising since persistent coughing at an intensity equivalent to 100% MVC is likely to be associated with symptoms such as syncope. Lasserson et al demonstrated differences in the patterns of muscle EMG activation between voluntary and induced cough [133]. The significant additional reserve in cough intensity during MVC may be due to voluntary recruitment and/or coordination of muscles that are capable of generating the high intra-abdominal pressures required for other functions such as vomiting or labour. EMG_{abdo}, P_{ga} and P_{oes} in spontaneous cough were comparable to those for capsaicin induced cough. Cough flow, however, was significantly lower in induced cough, 40% of that in spontaneous cough. The disproportionately low peak cough flow relative to pressure may suggest a failure of transmission of intra-thoracic pressure into flow during capsaicin induced cough. Future studies should investigate potential mechanisms for this. The physiological differences between induced and spontaneous cough may be important for explaining the differences in the efficacy of some antitussive drugs between pre-clinical models and clinical trials of patients with spontaneous cough.

The intensity of cough was well judged by most patients when asked to rate the intensity of voluntary cough. EMG, pressure and flow all correlated well with subjective ratings of cough intensity. The relationship between cough intensity VAS and pressure was marginally better than that with flow. Flow, however, is easier and more practical to measure because it is non-invasive. Flow may therefore be the objective measure of choice to assess cough intensity. The study of subjective ratings of cough intensity ought to be repeated in larger numbers and extended to spontaneous cough in patients with chronic cough. The mechanism by which the brain receives information relating to the perception of cough effort requires further investigation.

There were some limitations to this study. A relatively small number of patients were studied. The wide standard deviations seen in some measures, such as expiratory muscle strength and oesophageal pressure are likely to be due to the small sample size. It was not possible to analyse induced and spontaneous cough physiological data in each gender or disease category separately due to the numbers studied and it is possible that intensity could have differed according to the aetiology. However, the aim of this study was to investigate the intensity of cough in patients with an isolated chronic cough, irrespective of the underlying cause. The comparison between ER and cough was also limited by small numbers and needs clarification in larger studies. Patients with chronic cough had a slightly greater body mass index than healthy controls, which could have had an impact on the physiological parameters assessed, but further analysis did not demonstrate any relationship between BMI and PCFR, P_{ga} or P_{oes}. Male patients with cough took smaller inspired volumes than controls and it is possible that this resulted in failure to achieve true maximum voluntary cough. A further study standardising inspired volumes is warranted to clarify this. Single voluntary coughs were studied, but not bouts of voluntary coughs. Other investigators, however, have demonstrated that the intensity of cough is similar between single efforts and bouts [125]. Furthermore, the relationship between cough pressure and inspired volume and cough flow has been reported to be best for the first cough of a bout [125, 285]. Respiratory muscle strength was assessed with a non-volitional measure (Twitch T_{10} P_{ga}) to obviate the effect of motivation but future studies could also consider maximum expiratory pressure ($P_{E,max}$). Finally, whilst it is possible that the gastric pressure response to magnetic stimulation was not supramaximal, Twitch T_{10} P_{ga} is known to be a repeatable measure used by many other investigators and the control group Twitch T_{10} P_{ga} data was consistent with previous reports [217].

6.7 Conclusion

In conclusion, the intensity of voluntary cough is increased in patients with chronic cough. The mechanism for this is unclear but is unlikely to be due to an increase in expiratory muscle strength. Further studies should evaluate the larynx, particularly the compressive phase of cough. Physiological measures of the intensity of

voluntary cough correlate well with patients' subjective perception of cough intensity. Peak cough flow rate, oesophageal pressure and gastric pressure are important and relevant measures of cough intensity in patients with chronic cough.

7 The relationship between physiological measures of cough intensity and sound

7.1 Abstract

Rationale: In patients with chronic cough, the intensity of cough is an important determinant of global cough severity. Cough sound has been proposed as a measure of the intensity of coughs but few studies have validated its use against physiological measures.

Objectives: To investigate the relationship between cough sound and physiological measures of cough intensity in patients with chronic cough and healthy controls.

Methods: 17 patients with chronic cough and 15 healthy controls underwent contemporaneous measurements of cough sound, peak cough flow rate and oesophageal pressure. Cough sound was analysed for three time windows: phase 1 (P_1), phases 1-3 (P_{1-3}) and 0.5 second window from onset of phase 1 ($P_{0.5}$). A range of sound parameters was calculated for each time window (power (PW), peak energy (Ep), mean energy (Em), rise time, duration, peak frequency, bandwidth and centroid frequency). The relationships between sound and physiological measures were compared for P_1, P_{1-3} and $P_{0.5}$. The relationship between sound and subjective cough intensity visual analogue score (VAS) was evaluated in a subgroup. Repeatability of cough sounds and the effect of microphone position were also assessed.

Results: Sound power and energy correlated strongly with cough flow (median Spearman r 0.88, 0.87 and 0.89 for P_1 sound PW, Ep and Em respectively) and oesophageal pressure (median Spearman r 0.89, 0.89 and 0.90 for P_1 sound PW, Ep and Em respectively). There was little difference in strength of correlations between sound measures analysed from P_1, P_{1-3} or $P_{0.5}$. PW and energy were also strongly correlated with cough intensity VAS. PW, Ep and Em were highly repeatable (ICC 0.89-0.94). Power and energy were significantly affected by microphone position in all directions.

Conclusions: Cough sound power and energy correlate strongly with physiological measures of cough intensity and subjective perception of cough intensity. Analyses from phase 1 (P_1) or 0.5 second ($P_{0.5}$) time windows yield similar results, but the latter may be preferential due to the potential for automated analysis. Power and energy are highly repeatable measures but the microphone position is important and should be standardised and kept constant.

7.2 Introduction

In patients with chronic cough, the intensity of cough is an important determinant of global cough severity [140]. The intensity of cough can be assessed objectively with peak cough flow rate or oesophageal and gastric pressure. Limitations of cough flow and pressure are that they are either invasive or impractical to measure in an ambulatory setting. Recent technological advances have permitted the measurement of cough sounds continuously in the patients' own environment for the assessment of cough frequency [173]. Cough sound has been proposed as a measure of the intensity of coughs [184]. However, few studies have validated cough sound as a measure of cough intensity.

7.3 Aims

The aim of this study was to investigate the relationship between sound and physiological measures of cough intensity in patients with chronic cough and in healthy controls.

7.4 Methods

7.4.1 Subjects

Consecutive patients referred for investigation of a chronic cough were recruited from a respiratory outpatient clinic. All patients had cough for greater than 8 weeks and were symptomatic at the time of recruitment. The cause of cough was established following investigation and trials of treatment according to a standardised protocol [36]. Exclusion criteria were smokers or history of smoking within the past 1 year and upper respiratory tract infection within the previous 4

weeks. Healthy control subjects were recruited from local advertising. Exclusion criteria for control subjects in addition to those listed above included symptoms of cough, history of respiratory disease and abnormal lung function. Ethical approval was granted by the East London and the City Research Ethics Committee (10/H0703/6). All subjects gave informed consent.

7.4.2 Physiological measures of cough intensity

7.4.2.1 Cough flow rate

Respiratory flow was measured at the mouth using a Fleisch type pneumotachograph (P.K. Morgan ltd, Kent, UK) attached to a full-face mask (Hans Rudolph Inc, Kansas City, USA). The pneumotachograph was calibrated prior to each study by 2-point calibration with a rotameter. Peak cough flow rate (PCFR) was measured as the peak expiratory excursion during cough and expressed as a percentage of predicted peak expiratory flow rate ($PEFR_{Pred}$) to adjust for age, gender and height.

7.4.2.2 Cough oesophageal pressure

Thoracic (oesophageal pressure, P_{oes}) was measured in accordance with American Thoracic Society recommendations [231]. A balloon catheter (Cooper Surgical, Berlin, Germany) was inserted nasally and positioned within the lower oesophagus. The balloon catheter was attached to a pressure transducer (MP45; Validyne, Northridge, CA, USA) and signal amplifier (CD-280; Validyne). Cough P_{oes} was defined as the peak pressure during coughs.

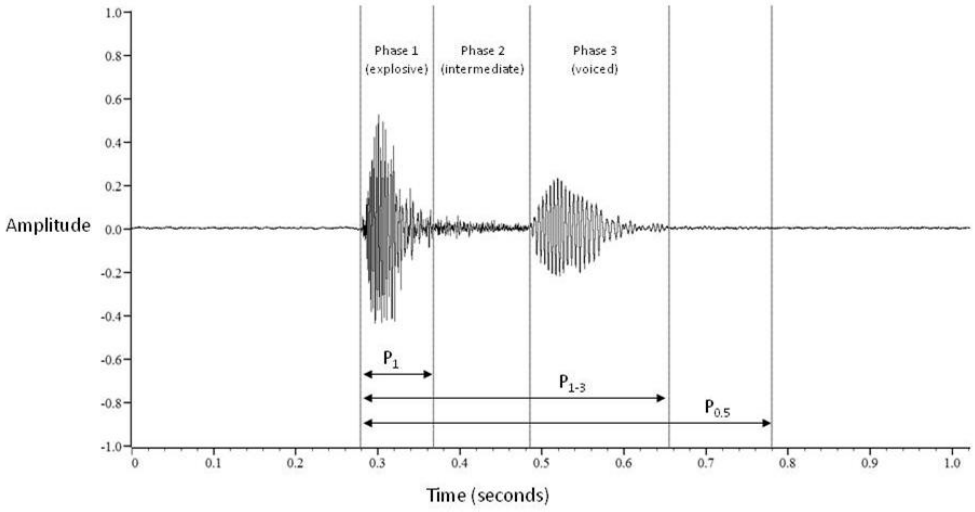
7.4.3 Cough sound

Cough sounds were recorded using a free-field microphone (MKE 2-5-C, Sennheiser, Wedermark, Germany) placed 20 cm inferior to the mouth and a pizo-electric contact microphone (3017, Philips Respironics, Surrey, UK) placed over the larynx. The positions of the microphones were standardised for all subjects. The recordings were sampled at a frequency of 8,000 Hz, amplified (free field microphone gain x10,

contact microphone gain x3) and digitally filtered between 20 Hz and 4,000 Hz (1902 signal conditioner, Cambridge Electronic Design, Cambridge, UK) [183].

A cough sound can comprise of up to 3 phases; explosive (phase 1), intermediate (phase 2) and voiced (phase 3), Figure 7-1. They correspond to glottal opening, steady-state flow and interruption of airflow due to narrowing of the glottis respectively [115]. Phase 3 is not always present and in its absence the identification of the termination of phase 2 becomes difficult due to the gradual dissipation of the signal [187, 188]. Therefore, the explosive phase (phase 1, P_1) was selected for primary analysis since it is the most consistently present and identifiable of all phases. The onset and end of P_1 was manually marked using Spike software (Figure 7-1). The duration from the onset of phase 1 to the end of phase 3, if present, ($P_{1\text{-}3}$) was also manually marked for analysis (Figure 7-1). Finally, cough sounds were analysed using a constant time duration, 0.5 seconds from onset of Phase 1 ($P_{0.5}$), since the mean duration of an entire cough sound (all phases) has previously been reported to fall within this duration (Figure 7-1) [192, 286]. $P_{0.5}$ was considered sufficiently brief to avoid overlap with adjacent coughs and would provide preliminary data for potential automated analysis of these measures.

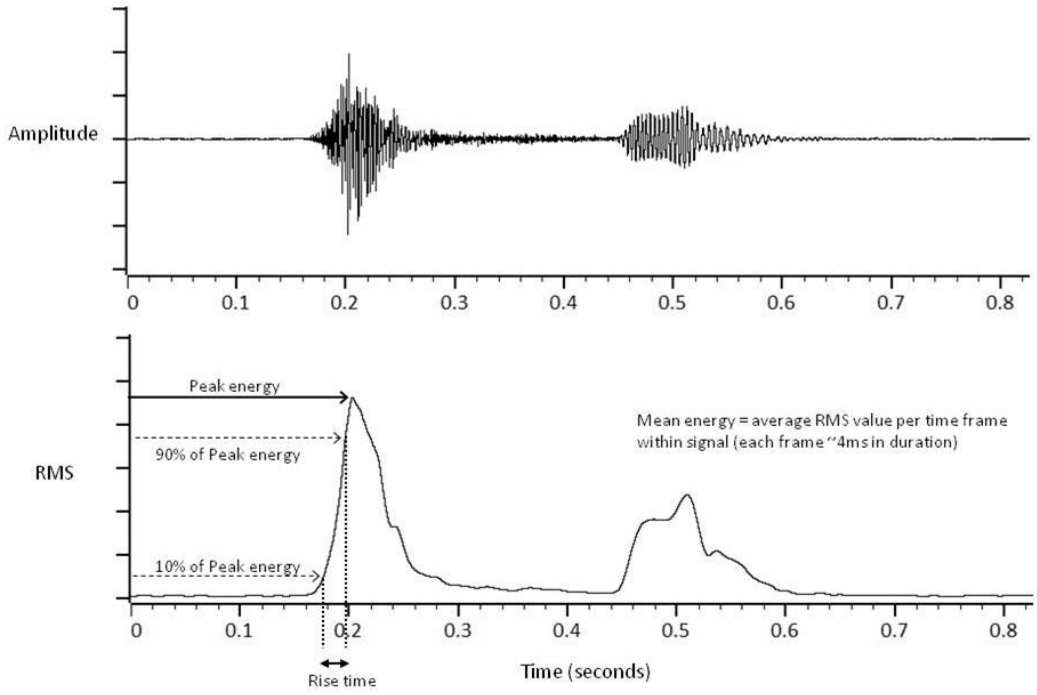
Figure 7-1 Phases of cough sound



Phases of classic 3-phase cough sound signal. T_{P1}: phase 1 time window; $T_{P1\text{-}3}$: phases 1-3 time window; $T_{0.5}$: 0.5 second time window.

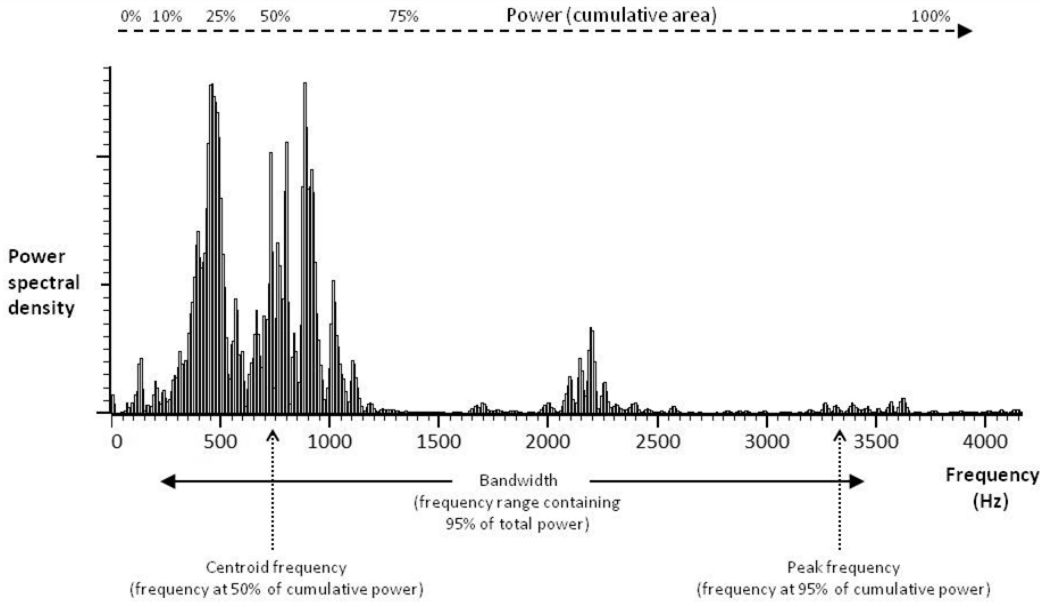
A custom script (MATLAB®, The MathWorks, Massachusetts, USA) was used to calculate the following sound parameters from the cough signal in a standardised manner: Peak energy (Ep), Mean energy (Em), rise time (RT), duration (D), power (PW), peak frequency (Fp), centroid frequency (Fc) and bandwidth (BW). Ep, Em and RT were calculated from the root mean square (RMS) of the cough signal in its time domain (to convert all values into positive values) (Figure 7-2) [260]. Ep was defined as the maximum value of the root mean square cough signal; Em was defined as the average RMS value per time frame of the cough signal (at a sampling frequency of 8,333 Hz, each time frame was approximately 3.84 ms in duration); and RT was defined as the duration of time taken for the RMS cough signal to rise from 10% to 90% of the peak energy value. PW, BW, Fp and Fc were calculated from the frequency spectrum of the cough signal following Fast Fourier Transformation (Figure 7-3) [187, 194]. PW was defined as the area under the curve (AUC) of the power spectral density (PSD); BW was defined as the frequency range or band containing 95% of the total spectral power; Fp was defined as the frequency at which 95% of the cumulative total spectral power was reached; and Fc was defined as the frequency at which the mass of the entire PSD signal spectrum was centred, that is, at 50% of the cumulative power (Figure 7-3).

Figure 7-2 Cough sound intensity parameters - time domain



Top trace depicting a typical cough sound signal in the time series domain and lower trace depicting the root mean square (RMS) derivative.

Figure 7-3 Frequency spectrum domain



Frequency spectrum domain of a typical cough sound signal following Fast Fourier Transformation.

7.4.4 Lung function

Spirometry and peak expiratory flow rate were measured in accordance with international guidelines [242, 243].

7.4.5 Protocol

7.4.5.1 Relationship between cough sound intensity and P_{oes} and peak cough flow

Subjects were instructed to perform at least 10 single maximum voluntary coughs (MVC) until cough P_{oes} reached a plateau and was repeatable. Sufficient time was allowed between cough efforts to avoid fatigue and to ensure the return of lung volume to functional residual capacity. Subjects were then asked to perform at least 10 voluntary coughs within each of the following quintiles of cough intensity: 0-20%, 21-40%, 41-60%, 61-80% and 81-100% of maximum voluntary cough P_{oes}. Real-time visual feedback with graphical demonstration of the P_{oes} trace on a computer screen was used to guide subjects. All coughs were recorded and analysed individually.

7.4.5.2 Repeatability

In order to assess the repeatability of cough sound measures, 10 healthy subjects (6 female) performed 10 maximum voluntary coughs on 2 occasions, 1 week apart. Cough peak flow rate and cough sounds were recorded using the free-field microphone. The microphone position was standardised for all subjects as described previously.

7.4.5.3 Microphone position

The impact of position of the microphone on cough sound measures was investigated by simultaneously recording cough sounds in 8 healthy subjects. 4 identical free-field microphones were placed in different positions relative to the mouth. The standard microphone position (centre) was located 20 cm inferior to the mouth. 3 additional microphones were positioned 5cm superior, inferior and lateral to the standard position (Figure 7-4). Subjects were asked to produce 10

voluntary coughs of similar intensity. The coefficients of variation of the cough sound measures were calculated for each subject in order to ensure repeatability of the series of coughs. A coefficient of variation less than 10% was considered acceptable. The mean values for the sound parameters from each microphone position were compared.

Figure 7-4 Microphone position

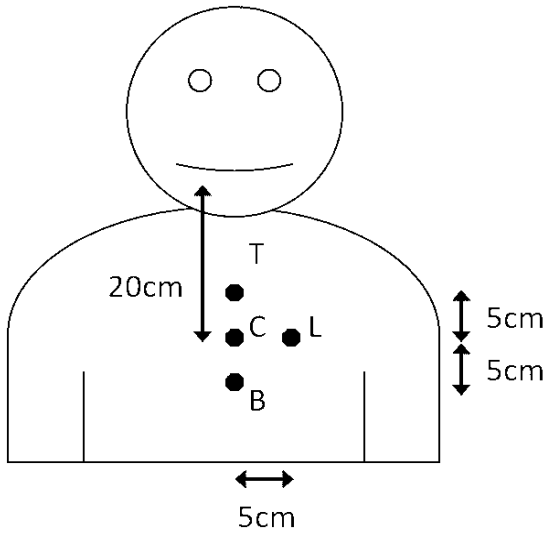


Figure depicting positions of microphone for investigation of effect on cough sound measures. Centre microphone positioned 20 cm inferiorly to mouth. T: top; C: centre; B: bottom; L: left.

7.4.5.4 Relationship between cough sound and subjective assessment of cough intensity

A subgroup of 8 subjects with chronic cough was instructed to produce at least 10 single voluntary coughs of varying intensity in a random order. Subjects were blinded to all physiological and sound measures of cough. After each cough effort, subjects were asked to subjectively rate the intensity of the cough on a 100 mm VAS scale. VAS scores and cough intensity measures for all coughs were then compared for each subject.

7.4.6 Analysis

Physiological and sound data for coughs were time synchronised, converted from analogue to digital format (Micro 1401 mk II; Cambridge Electronic Design, Cambridge, UK) and analysed with Spike 2 version 6 software (Cambridge Electronic Design, Cambridge, UK) on a computer. Statistical analysis was performed using SPSS version 19 (IBM) and Prism version 5 (GraphPad). Appropriate parametric or non-parametric tests were used depending on distribution of the data. Within-subject correlations were calculated between cough sound parameters and physiological measures (PCFR:$PEFR_{pred}$ and P_{oes}) using Spearman correlation coefficients. To demonstrate a correlation coefficient $\rho=0.5$ between cough sound and peak cough flow rate or P_{oes} against a null hypothesis of $\rho=0$ with 80% power and 5% error, a sample size of 29 subjects was required. To assess repeatability, intra-class correlation coefficients (2-way average) were calculated for the cough sound parameters between visits 1 and 2. In order to study the impact of microphone position on cough sound intensity, an analysis of variance (ANOVA) was performed for cough sound parameters from each microphone position, and paired t-tests between the centre and other positions. All sound analyses were derived from the free-field microphone unless otherwise stated.

7.5 Results

17 patients with chronic cough and 15 healthy subjects were recruited. Baseline characteristics are given in Table 7-1. The causes of cough in patients were asthma (24%), gastro-oesophageal reflux disease (24%), eosinophilic bronchitis (6%), post-infectious (6%), bronchiectasis (6%) and idiopathic (35%).

1058 coughs from patients and 758 coughs from healthy subjects were recorded and analysed. The maximum peak cough flow, P_{oes} and key sound measures during MVC are presented in Table 7-2.

Table 7-1 Subject characteristics

Characteristic	Patients n=17	Controls n=15	P-value
Male (n, %)	6 (35)	7 (47)	0.720
Age (years)	55 ± 16	47 ± 21	0.317
BMI ($kg.m^{-2}$)	28 ± 7	24 ± 1	0.101
FEV_1 (% predicted)	96 ± 17	100 ± 17	0.541
FVC (% predicted)	107 ± 18	108 ± 20	0.855
FEV_1/FVC (%)	75 ± 7	78 ± 8	0.301
Duration of cough (months)	34 (24-85)	-	-

Data presented as mean ± SD, n (%) or median (IQR). BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Table 7-2 Physiological and sound measures during maximum voluntary cough

	Patients	Controls	P-value
PCFR (L/min)	653 ± 200	674 ± 288	0.808
PCFR:PEFRpred	1.50 ± 0.36	1.44 ± 0.46	0.674
P_{oes} (cmH_2O)	184 ± 48	155 ± 52	0.115
Free Field microphone			
PW	47.6 ± 1.7	49.6 ± 2.0	0.457
PW coefficient of variation	14.9%	16.0%	
Ep	1.09 ± 0.74	1.30 ± 1.06	0.792
Ep coefficient of variation	67.6%	81.6%	
Contact microphone			
PW	39.2 ± 7.4	42.9 ± 8.0	0.308
PW coefficient of variation	18.8%	18.6%	
Ep	0.39 ± 0.26	0.57 ± 0.40	0.308
Ep coefficient of variation	68.1%	70.6%	

Data presented as mean ± SD. Cough sound analysed from phase 1 (P_1) of cough sound. PCFR: peak cough flow rate; PCFR:$PEFR_{pred}$: peak cough flow rate normalised to predicted peak expiratory flow rate; P_{oes}: oesophageal pressure; PW: power; Ep: peak energy.

7.5.1 Relationship between physiological and cough sound measures

7.5.1.1 Flow

The correlation coefficients between PCFR:$PEFR_{pred}$ and sound measures derived from P_1, $P_{1\text{-}3}$ and $P_{0.5}$ are presented in Table 7-3. The sound parameters with the strongest correlations with PCFR:$PEFR_{pred}$ were power (PW), peak energy (Ep) and mean energy (Em) (Table 7-3). The median (interquartile range) within-subject correlation coefficient between sound PW and PCFR:$PEFR_{pred}$ was 0.88 (0.78-0.93), all individual subject p-values <0.001 (Table 7-3). These relationships remained strong when patients, controls and gender were analysed separately (Table 7-4 to Table 7-6). A representative example is shown in Figure 7-5. The correlations between sound power and energy and PCFR:$PEFR_{pred}$ were marginally superior with the free-field microphone compared with the contact microphone (Table 7-4 and Table 7-7).

Table 7-3 The relationship between cough sound, flow and oesophageal pressure

a) Flow

Sound parameter	Sound analysis time window		
	P_1	P_{1-3}	$P_{0.5}$
PW	0.88 (0.78-0.93)	0.82 (0.60-0.90)	0.88 (0.79-0.92)
Ep	0.87 (0.78-0.92)	0.81 (0.56-0.90)	0.87 (0.79-0.91)
Em	0.89 (0.78-0.92)	0.79 (0.38-0.89)	0.87 (0.79-0.92)
RT	0.31 (0.02-0.48)	0.01 (-0.18-0.3)	0.23 (-0.05-0.42)
D	0.29 (-0.11-0.59)	0.60 (0.23-0.82)	-0.02 (-0.19-0.16)
Fp	0.11 (-0.25-0.34)	0.35 (0.07-0.53)	0.17 (-0.06-0.45)
BW	-0.24 (-0.53-0.11)	0.05 (-0.16-0.35)	-0.10 (-0.35-0.19)
Fc	0.49 (0.25-0.71)	0.63 (0.26-0.79)	0.48 (0.19-0.78)

b) Oesophageal pressure

Sound parameter	Sound analysis time window		
	P_1	P_{1-3}	$P_{0.5}$
PW	0.89 (0.84-0.95)	0.85 (0.65-0.91	0.89 (0.81-0.94)
Ep	0.89 (0.82-0.95)	0.85 (0.58-0.93)	0.89 (0.82-0.94)
Em	0.90 (0.80-0.94)	0.80 (0.45-0.87)	0.88 (0.83-0.95)
RT	0.35 (-0.04-0.45)	0.05 (-0.33-0.53)	0.23 (-0.13-0.5)
D	0.23 (-0.11-0.54)	0.70 (0.47-0.84)	0.01 (-0.15-0.18)
Fp	0.06 (-0.30-0.41)	0.36 (0.12-0.60)	0.26 (-0.11-0.46)
BW	-0.40 (-0.58-0.10)	0.06 (-0.13-0.39)	-0.15 (-0.43-0.24)
Fc	0.53 (0.22-0.76)	0.68 (0.48-0.82)	0.53 (0.25-0.80)

Data presented as median (IQR) within-subject Spearman correlation coefficients for patients with chronic cough and healthy controls combined. Sound recorded with free-field microphone. The correlations were similar when patients and controls were analysed separately (Table 7-4 to Table 7-6). PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-4 The relationship between P_1 cough sound, flow and oesophageal pressure

a) Flow

P_1 sound parameter	All subjects	Females	Males	Patients	Controls
PW	0.88 (0.78-0.93)	0.83 (0.78-0.92)	0.92 (0.87-0.95)	0.79 (0.76-0.92)	0.89 (0.85-0.95)
Ep	0.87 (0.78-0.92)	0.84 (0.77-0.89)	0.91 (0.86-0.96)	0.82 (0.76-0.92)	0.89 (0.86-0.95)
Em	0.89 (0.78-0.92)	0.85 (0.74-0.92)	0.91 (0.88-0.95)	0.79 (0.73-0.92)	0.89 (0.87-0.94)
RT	0.31 (0.02-0.48)	0.29 (0.05-0.42)	0.33 (-0.02-0.48)	0.28 (-0.08-0.43)	0.41 (0.12-0.48)
D	0.29 (-0.11-0.59)	0.15 (-0.21-0.60)	0.43 (-0.11-0.62)	0.47 (-0.08-0.69)	0.02 (-0.17-0.43)
Fp	0.11 (-0.25-0.34)	0.18 (-0.24-0.34)	0.10 (-0.28-0.49)	0.03 (-0.22-0.32)	0.28 (-0.27-0.45)
BW	-0.24 (-0.53-0.11)	-0.22 (-0.54-0.11)	-0.41 (-0.57-0.09)	-0.26 (-0.63-0.02)	-0.16 (-0.53-0.11)
Fc	0.49 (0.25-0.71)	0.47 (0.18-0.68)	0.61 (0.29-0.75)	0.47 (0.21-0.67)	0.62 (0.24-0.83)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between P_1 cough sound and cough flow. Sound recorded with free-field microphone. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-4 The relationship between P_1 cough sound from a free-field microphone, flow and oesophageal pressure

b) Oesophageal pressure

P_1 sound parameter	All subjects	Females	Males	Patients	Controls
PW	0.89 (0.84-0.95)	0.87 (0.81-0.91)	0.94 (0.88-0.96)	0.88 (0.85-0.94)	0.91 (0.82-0.95)
Ep	0.89 (0.82-0.95)	0.84 (0.81-0.91)	0.94 (0.88-0.96)	0.84 (0.81-0.94)	0.91 (0.86-0.95)
Em	0.90 (0.80-0.94)	0.85 (0.77-0.92)	0.94 (0.87-0.95)	0.87 (0.78-0.94)	0.92 (0.85-0.94)
RT	0.35 (-0.04-0.45)	0.35 (-0.02-0.42)	0.40 (-0.06-0.48)	0.35 (-0.14-0.45)	0.36 (0.07-0.46)
D	0.23 (-0.11-0.54)	0.10 (-0.26-0.51)	0.37 (-0.07-0.61)	0.51 (-0.03-0.55)	-0.05 (-0.26-0.42)
Fp	0.06 (-0.30-0.41)	0.16 (-0.3-0.43)	0.00 (-0.31-0.53)	0.05 (-0.31-0.38)	0.08 (-0.29-0.47)
BW	-0.40 (-0.58-0.10)	-0.43 (-0.59-0.10)	-0.34 (-0.64-0.11)	-0.34 (-0.70-0.10)	-0.43 (-0.52-0.11)
Fc	0.53 (0.22-0.76)	0.52 (0.20-0.80)	0.64 (0.26-0.76)	0.52 (0.24-0.78)	0.64 (0.22-0.76)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between P_1 cough sound and oesophageal pressure. Sound recorded with free-field microphone. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-5 The relationship between P_{1-3} cough sound, flow and oesophageal pressure

a) Flow

P_{1-3} sound parameter	All subjects	Females	Males	Pts	Controls
PW	0.82 (0.60-0.90)	0.80 (0.56-0.90)	0.85 (0.63-0.94)	0.79 (0.59-0.89)	0.83 (0.65-0.95)
Ep	0.81 (0.56-0.90)	0.79 (0.49-0.89)	0.84 (0.59-0.96)	0.77 (0.55-0.87)	0.89 (0.60-0.96)
Em	0.79 (0.38-0.89)	0.79 (0.38-0.88)	0.80 (0.21-0.92)	0.73 (0.45-0.87)	0.80 (0.31-0.93)
RT	0.01 (-0.18-0.3)	-0.03 (-0.25-0.29)	0.16 (-0.18-0.60)	-0.05 (-0.18-0.27)	0.27 (-0.21-0.56)
D	0.60 (0.23-0.82)	0.59 (0.23-0.78)	0.64 (0.22-0.84)	0.58 (0.24-0.77)	0.66 (0.23-0.83)
Fp	0.35 (0.07-0.53)	0.16 (-0.21-0.43)	0.39 (0.27-0.63)	0.34 (0.07-0.53)	0.38 (0.03-0.57)
BW	0.05 (-0.16-0.35)	-0.08 (-0.38-0.10)	0.30 (0.21-0.38)	-0.03 (-0.21-0.28)	0.22 (-0.02-0.45)
Fc	0.63 (0.26-0.79)	0.41 (0.07-0.79)	0.67 (0.52-0.78)	0.64 (0.35-0.79)	0.57 (0.11-0.77)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between P_{1-3} cough sound and cough flow. Sound recorded with free-field microphone. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-5 The relationship between P_{1-3} cough sound, flow and oesophageal pressure

b) Oesophageal pressure

P_{1-3} sound parameter	All subjects	Females	Males	Pts	Controls
PW	0.85 (0.65-0.91)	0.85 (0.65-0.89)	0.90 (0.63-0.96)	0.85 (0.59-0.89)	0.88 (0.67-0.95)
Ep	0.85 (0.58-0.93)	0.82 (0.58-0.88)	0.93 (0.49-0.97)	0.82 (0.49-0.88)	0.90 (0.58-0.97)
Em	0.80 (0.45-0.87)	0.78 (0.46-0.85)	0.84 (0.44-0.93)	0.79 (0.44-0.84)	0.84 (0.43-0.93)
RT	0.05 (-0.33-0.53)	-0.05 (-0.35-0.45)	0.20 (-0.21-0.65)	-0.06 (-0.35-0.32)	0.38 (-0.20-0.70)
D	0.70 (0.47-0.84)	0.72 (0.45-0.82)	0.70 (0.59-0.85)	0.64 (0.45-0.80)	0.76 (0.52-0.85)
Fp	0.36 (0.12-0.60)	0.16 (-0.11-0.53)	0.43 (0.23-0.73)	0.31 (0.16-0.56)	0.39 (0.09-0.62)
BW	0.06 (-0.13-0.39)	-0.05 (-0.24-0.21)	0.32 (0.00-0.46)	-0.06 (-0.30-0.28)	0.29 (-0.03-0.43)
Fc	0.68 (0.48-0.82)	0.60 (0.23-0.77)	0.69 (0.60-0.87)	0.69 (0.31-0.79)	0.66 (0.60-0.86)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between P_{1-3} cough sound and oesophageal pressure. Sound recorded with free-field microphone. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-6 The relationship between $P_{0.5}$ cough sound, flow and oesophageal pressure

a) Flow

$P_{0.5}$ sound parameter	All subjects	Females	Males	Patients	Controls
PW	0.88 (0.79-0.92)	0.85 (0.77-0.90)	0.93 (0.83-0.96)	0.80 (0.77-0.91)	0.91 (0.85-0.96)
Ep	0.87 (0.79-0.91)	0.81 (0.78-0.87)	0.91 (0.84-0.95)	0.81 (0.76-0.90)	0.89 (0.82-0.95)
Em	0.87 (0.79-0.92)	0.85 (0.77-0.91)	0.92 (0.84-0.95)	0.84 (0.76-0.92)	0.91 (0.85-0.95)
RT	0.23 (-0.05-0.42)	0.17 (-0.07-0.32)	0.25 (-0.05-0.51)	0.10 (-0.06-0.33)	0.27 (0.04-0.48)
D	N/A	N/A	N/A	N/A	N/A
Fp	0.17 (-0.06-0.45)	0.27 (-0.25-0.45)	0.14 (-0.01-0.50)	0.13 (-0.05-0.40)	0.38 (-0.25-0.47)
BW	-0.10 (-0.35-0.19)	-0.10 (-0.44-0.21)	-0.19 (-0.32-0.12)	-0.10 (-0.34-0.13)	-0.03 (-0.46-0.26)
Fc	0.48 (0.19-0.78)	0.36 (0.16-0.79)	0.51 (0.21-0.79)	0.36 (0.18-0.61)	0.65 (0.19-0.81)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between $P_{0.5}$ cough sound and cough flow. Sound recorded with free-field microphone. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-6 The relationship between $P_{0.5}$ cough sound, flow and oesophageal pressure

b) Oesophageal pressure

$P_{0.5}$ sound parameter	All subjects	Females	Males	Patients	Controls
PW	0.89 (0.81-0.94)	0.87 (0.76-0.89)	0.94 (0.92-0.96)	0.89 (0.79-0.92)	0.89 (0.83-0.96)
Ep	0.89 (0.82-0.94)	0.84 (0.80-0.89)	0.94 (0.88-0.96)	0.88 (0.82-0.93)	0.89 (0.80-0.96)
Em	0.88 (0.83-0.95)	0.85 (0.78-0.89)	0.95 (0.91-0.96)	0.89 (0.83-0.92)	0.88 (0.84-0.96)
RT	0.23 (-0.13-0.50)	0.11 (-0.24-0.37)	0.25 (-0.11-0.56)	0.11 (-0.19-0.50)	0.25 (0.01-0.52)
D	N/A	N/A	N/A	N/A	N/A
Fp	0.26 (-0.11-0.46)	0.32 (-0.14-0.47)	0.13 (-0.04-0.55)	0.23 (-0.10-0.42)	0.30 (-0.14-0.53)
BW	-0.15 (-0.43-0.24)	-0.13 (-0.46-0.32)	-0.19 (-0.39-0.12)	-0.19 (-0.41-0.18)	-0.03 (-0.48-0.32)
Fc	0.53 (0.25-0.80)	0.50 (0.25-0.79)	0.65 (0.24-0.82)	0.50 (0.28-0.71)	0.61 (0.18-0.87)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between $P_{0.5}$ cough sound and oesophageal pressure. Sound recorded with free-field microphone. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-7 The relationship between P_1 cough sound from a contact microphone, flow and oesophageal pressure

a) Flow

P_1 sound parameter	All subjects	Females	Males	Patients	Controls
PW	0.82 (0.71-0.91)	0.79 (0.68-0.89)	0.89 (0.78-0.93)	0.82 (0.74-0.91)	0.81 (0.68-0.89)
Ep	0.83 (0.74-0.90)	0.80 (0.72-0.89)	0.89 (0.82-0.92)	0.82 (0.75-0.90)	0.84 (0.72-0.89)
Em	0.81 (0.72-0.90)	0.75 (0.70-0.86)	0.89 (0.77-0.92)	0.81 (0.73-0.92)	0.81 (0.70-0.89)
RT	0.20 (-0.06-0.35)	0.19 (-0.09-0.33)	0.21 (0.05-0.46)	0.15 (-0.09-0.43)	0.21 (0.14-0.33)
D	0.29 (-0.11-0.59)	0.15 (-0.21-0.60)	0.43 (-0.11-0.62)	0.47 (-0.08-0.69)	0.02 (-0.17-0.43)
Fp	0.20 (-0.19-0.62)	0.15 (-0.21-0.39)	0.57 (0.01-0.76)	0.17 (-0.17-0.52)	0.39 (-0.21-0.72)
BW	-0.09 (-0.46-0.33)	-0.17 (-0.48-0.08)	0.03 (-0.24-0.41)	-0.09 (-0.52-0.23)	0.01 (-0.42-0.33)
Fc	0.68 (0.33-0.86)	0.49 (0.10-0.71)	0.86 (0.70-0.91)	0.62 (0.36-0.72)	0.81 (0.11-0.92)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between P_1 cough sound and cough flow. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

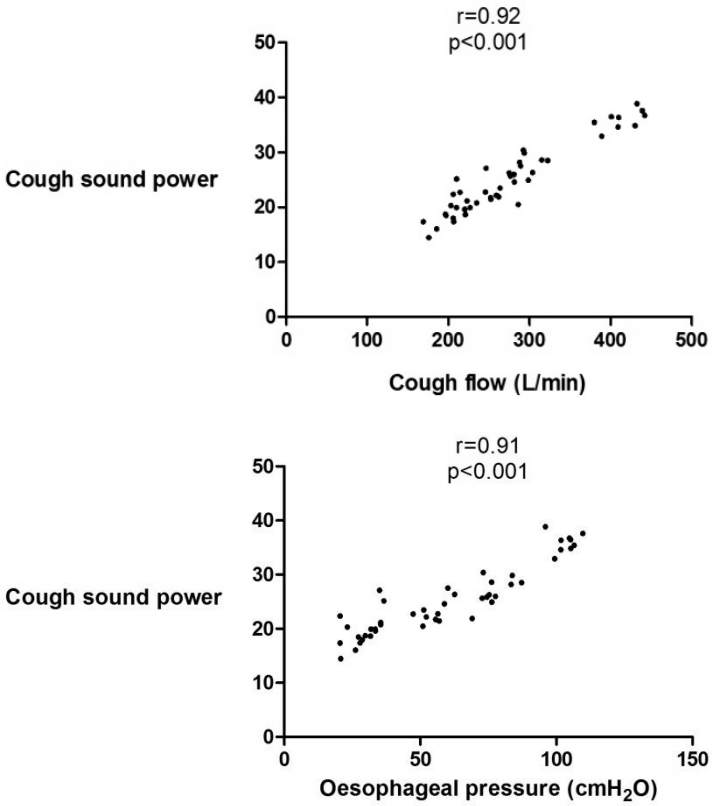
Table 7-7 The relationship between P_1 cough sound from a contact microphone, flow and oesophageal pressure

b) Oesophageal pressure

P_1 sound parameter	All subjects	Females	Males	Patients	Controls
PW	0.86 (0.76-0.90)	0.83 (0.70-0.88)	0.90 (0.86-0.94)	0.88 (0.81-0.92)	0.83 (0.68-0.90)
Ep	0.86 (0.79-0.90)	0.83 (0.75-0.89)	0.90 (0.87-0.93)	0.89 (0.82-0.92)	0.84 (0.75-0.90)
Em	0.85 (0.77-0.90)	0.85 (0.72-0.88)	0.88 (0.83-0.93)	0.88 (0.85-0.93)†	0.80 (0.72-0.88)
RT	0.21 (-0.07-0.42)	0.21 (-0.08-0.45)	0.28 (0.06-0.48)	0.22 (-0.12-0.48)	0.20 (0.03-0.45)
D	0.23 (-0.11-0.54)	0.10 (-0.26-0.51)	0.37 (-0.07-0.61)	0.51 (-0.03-0.55)	-0.05 (-0.26-0.42)
Fp	0.21 (-0.19-0.73)	0.08 (-0.25-0.49)	0.68 (0.05-0.81)	0.18 (-0.17-0.55)	0.41 (-0.21-0.81)
BW	-0.13 (-0.45-0.36)	-0.18 (-0.51-0.16)	0.06 (-0.24-0.55)	-0.14 (-0.45-0.26)	-0.10 (-0.45-0.49)
Fc	0.71 (0.43-0.92)	0.58 (0.22-0.74)	0.91 (0.74-0.94)	0.64 (0.43-0.84)	0.88 (0.17-0.94)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between P_1 cough sound and oesophageal pressure. Peak cough flow rate normalised to predicted peak expiratory flow rate. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Figure 7-5 Relationship between cough sound and cough oesophageal pressure and flow in an individual patient with chronic cough



Patient is a representative example. Cough sound power calculated from P_1 time window. Spearman correlation coefficients.

7.5.1.2 Pressure

The correlation coefficients between P_{oes} and sound measures derived from P_1, $P_{1\text{-}3}$ and $P_{0.5}$ are presented in Table 7-3. The strongest relationships with P_{oes} were found with PW, Ep and Em. The median (IQR) within-subject correlation coefficient between PW and P_{oes} was 0.89 (0.84-0.95), all individual subject p-values <0.001 (

Table 7-3 and Figure 7-5). The correlations between sound measures and P_{oes} were similar to those with flow (Table 7-3). The correlations were also similar when patients, controls and gender were analysed separately (Table 7-4 to Table 7-6).

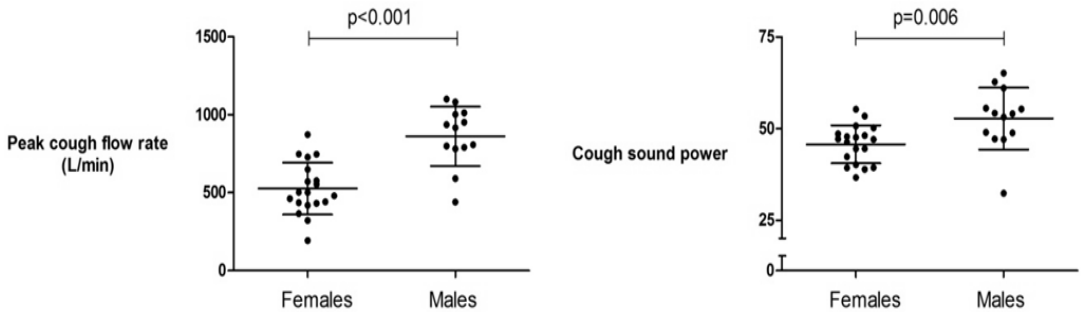
7.5.2 Relationship between physiological and sound measures using a constant time-window ($P_{0.5}$)

The correlation coefficients between cough sound PW, Ep and Em evaluated from a 0.5-second time-window ($P_{0.5}$) and cough flow and pressure were strong for all subjects (median correlation coefficient between PW, Ep and Em and cough flow 0.88, 0.87 and 0.87 respectively and between PW, Ep and Em and pressure 0.89, 0.89 and 0.88 respectively). These correlations were comparable to those evaluated from cough sound phase 1 and phase 1-3 (Table 7-3).

7.5.3 Clinical characteristics affecting cough sound

PW was selected for further analysis since it had a marginally superior relationship with flow and pressure (Table 7-4). Cough sound measures from free-field microphones were used in preference to contact microphones because of their marginally stronger correlations with cough flow (Table 7-4 and Table 7-7). Sound PW during MVC was significantly higher in males compared with females (mean ± SD PW 52.7 ± 8.4 vs. 45.7 ± 5.2, difference between means 7.1, 95% CI 2.2-12.0, p=0.006) (Figure 7-6). PW during MVC was not associated with age (ρ=-0.26), weight (ρ=0.15), BMI (ρ=-0.06), or FVC (ρ=0.34), and only weakly associated with height (ρ=0.39, p=0.026) and FEV_1 (ρ=0.39, p=0.026). Subgroup analyses for individual diagnostic categories of cough were not performed due to sample size limitations.

Figure 7-6 Gender differences in cough flow and sound during maximum voluntary cough

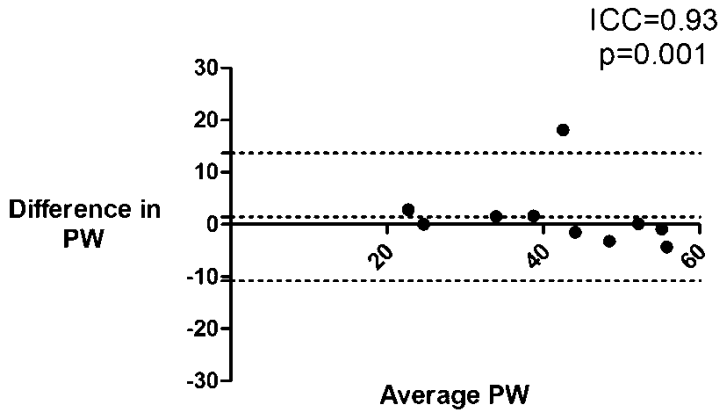


Data presented as mean ± SD. Cough sound power calculated from phase 1 time window (P_1) from free-field microphone.

7.5.4 Repeatability of cough sound measures

The intraclass correlation coefficients (ICC) for cough sound PW, Ep and Em derived from P_1 on two occasions were good (ICC 0.93, 0.94 and 0.89 respectively, all p-values <0.01; Figure 7-7 and Table 7-8). For $P_{0.5}$, the repeatability of PW and Ep were good (ICC 0.93 and 0.94, p≤0.001) but was weaker for Em (ICC 0.74, p=0.030; Table 7-8). There were no significant differences in sound PW between visits 1 and 2 for P_1 (p=0.489) or $P_{0.5}$ (p=0.408).

Figure 7-7 Repeatability of cough sound power during maximum voluntary cough



Bland-Altman plot of cough sound power during maximum voluntary cough on two separate occasions. Power taken from free-field microphone. PW: power; ICC: intraclass correlation coefficient.

Table 7-8 Repeatability of cough sound measures during maximum voluntary cough

	ICC	P-value
Phase 1, P_1		
PW	0.93	<0.001
Ep	0.94	<0.001
Em	0.89	0.002
0.5-second time-window, $P_{0.5}$		
PW	0.93	<0.001
Ep	0.94	<0.001
Em	0.74	0.030

Data presented as intraclass correlation coefficients (ICC). Sound recorded with free-field microphone. PW: power; Ep: peak energy; Em: mean energy.

7.5.5 Effect of microphone position on cough sound measures

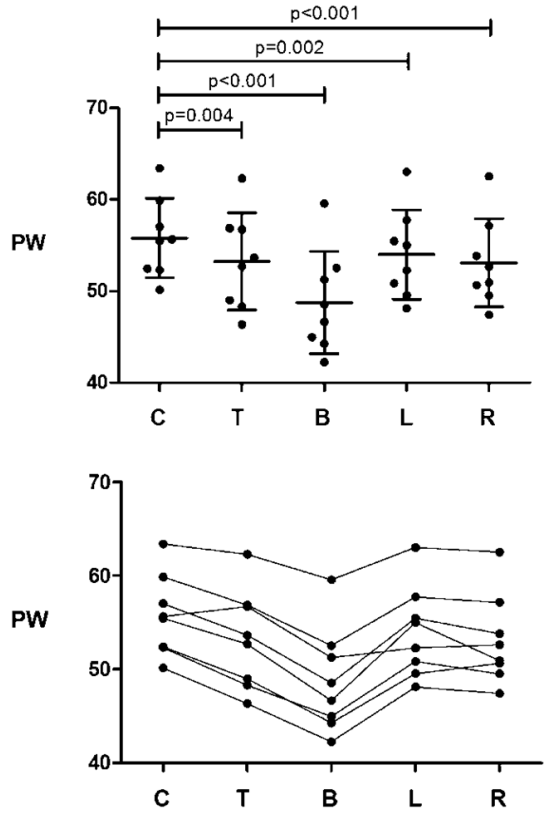
For all subjects, the coefficient of variation of cough sound PW for the 10 coughs was less than 10%, suggesting that the series of coughs were of similar intensity. Mean cough sound PW was greatest in the standard centre position (Table 7-9). There was a significant difference in mean PW between the centre position and all other positions (ANOVA, p<0.001) and the difference was greatest between the centre position and the bottom position (Table 7-9 and Figure 7-8).

Table 7-9 The impact of microphone position on cough sound power

	Cough sound power	P-value vs. Centre
Centre	55.8 ± 4.3	-
Top	53.3 ± 5.3	0.004
Bottom	48.8 ± 5.6	<0.001
Left	54.0 ± 4.9	0.002
Right	53.1 ± 4.8	<0.001

Data presented as mean ± SD and paired t-test p-values. Data is for P_1 sound power recorded with free-field microphone.

Figure 7-8 Effect of microphone position on cough sound power



Upper graph shows mean ± SD sound power for each microphone position. Lower graph demonstrates the matched values for each subject. PW: power; C: centre; T: top; B: bottom; L: left; R: right.

7.5.6 Relationship between cough sound and subjective assessment of cough intensity

The median correlation coefficients between cough sound measures and subjective cough intensity visual analogue score are presented in Table 7-10. Individual p-values for P_1 sound are given in Table 7-11. The correlations were strongest for PW, Ep and Em. The correlations for constant time duration $P_{0.5}$ were similar to those for phase 1 (P_1). The relationships between free-field microphone derived cough sounds were generally better than those from the contact microphone (Table 7-10).

Table 7-10 The relationship between cough sound measures and subjective cough intensity visual analogue score in patients with chronic cough

a) Phase 1, P_1

P_1 sound parameter	**Correlation with cough intensity VAS**	
	Free-field microphone	Contact microphone
PW	0.84 (0.69-0.96)	0.76 (0.4273-0.90)
Ep	0.86 (0.64-0.93)	0.62 (0.53-0.88)
Em	0.76 (0.58-0.97)	0.67 (0.45-0.91)
RT	0.29 (-0.04-0.78)	0.31 (-0.24-0.69)
D	0.47 (0.20-0.75)	0.47 (0.20-0.75)
Fp	0.32 (0.24-0.71)	0.70 (0.11-0.88)
BW	0.10 (-0.20-0.30)	0.06 (-0.33-0.80)
Fc	0.44 (0.16-0.87)	0.71 (0.62-0.79)

b) 0.5-second time-window, $P_{0.5}$

$P_{0.5}$ sound parameter	**Correlation with cough intensity VAS**	
	Free-field microphone	Contact microphone
PW	0.88 (0.67-0.90)	0.83 (0.46-0.85)
Ep	0.77 (0.61-0.88)	0.68 (0.52-0.88)
Em	0.86 (0.65-0.90)	0.71 (0.31-0.91)
RT	0.32 (-0.09-0.66)	0.44 (-0.02-0.71)
D	0.17 (0.00-0.31)	0.17 (0.00-0.31)
Fp	0.43 (0.21-0.65)	0.30 (0.00-0.64)
BW	0.03 (-0.62-0.32)	0.12 (-0.24-0.39)
Fc	0.34 (0.06-0.72)	0.66 (0.31-0.78)

Data presented as median (IQR) within-subject Spearman's correlation coefficients between cough sound and cough intensity visual analogue score (VAS). Individual correlation coefficients for P_1 sound are presented in Table 7-11. PW: power; Ep: peak energy; Em: mean energy; RT: rise time; D: duration; Fp: peak frequency; BW: bandwidth; Fc: centroid frequency.

Table 7-11 Individual correlation coefficients between cough sound and cough intensity visual analogue score

P_1	Subject							
Sound parameter	1	2	3	4	5	6	7	8
PW	0.85*	0.67*	0.38	0.82*	0.99*	0.73*	0.89*	0.98*
Ep	0.70*	0.62	0.43	0.77*	0.98*	0.84*	0.88*	0.95*
Em	0.72*	0.54	0.41	0.73*	0.99*	0.80*	0.91*	0.99*
RT	0.44	-0.09	0.12	0.78*	0.90*	-0.3	0.77*	0.14
D	0.78*	0.15	0.41	0.66*	0.36	0.12	0.81*	0.54
Fp	0.25	0.33	0.83*	0.32	0.76*	0.24	0.55*	-0.16
BW	-0.64*	0.31	0.22	-0.15	0.26	-0.03	0.31	-0.21
Fc	0.15	0.24	0.90*	0.18	0.65*	0.81*	0.89*	-0.56

*Data presented as individual Spearman correlation coefficients between cough sound and cough intensity visual analogue score (VAS). Sound recorded with free field microphone and measures derived from P_1 time window. *: $p<0.05$.*

7.6 Discussion

This study has shown that cough sound power, peak energy and mean energy correlate strongly with peak cough flow rate and oesophageal pressure during voluntary cough. There was little difference in the strength of correlation between physiological measures and sound measures analysed from the first phase of cough sound, all three phases or a 0.5-second constant time window. Sound power and energy were strongly associated with subjective cough intensity visual analogue scores. The performance of sound measures from the free field microphone was marginally superior to that of sound measures from the contact microphone.

Cough sounds have been studied by a number of investigators, but few have evaluated their potential as a measure of cough intensity [194-196, 241]. Pavesi et al used sound power as a measure of cough effort in a randomised controlled trial of dextromethorphan in acute cough but they did not assess the validity of PW for this purpose [183, 184]. To my knowledge, few studies have validated cough sound measures against a physiological measure of cough intensity.

The sound parameters selected for evaluation were chosen based on previous studies and knowledge of their properties [189, 196, 260, 287]. The parameters were derived from the time domain and the frequency spectrum domain (following Fast Fourier Transformation, FFT) of the cough sound signal. FFT is a widely used method for assessing power spectral density [183, 184, 187]. In this study, sound power, peak energy and mean energy had the best correlations with cough flow and oesophageal pressure. The data suggests that sound power may be better than energy since there was less variation during maximum voluntary coughs. Thorpe et al also reported a relationship between total power and peak flow of first cough phase, but the correlation was weak (ρ=0.42) [187]. However, they performed a group analysis of 114 voluntary coughs from 12 asthmatic and 5 healthy children of different ages. In contrast, I assessed within-subject correlations between sound and flow for an average of 57 coughs per subject. The other sound parameters such as peak frequency and centroid frequency had weaker relationships with flow, but there was a wide variation in strength of the association between individual subjects.

The sound parameters were calculated for three pre-defined time windows within the cough signal (Phase 1, Phases 1-3 and constant 0.5-second duration from onset of Phase 1). It was found that there was little difference between P_1 and $P_{1\text{-}3}$ in their relationship with flow and pressure. This may be because P_1 contains the majority of the energy in cough sounds [260]. P_1 has the advantage of being present in all cough sounds, whereas the third phase in missing in some coughs [187]. However, the required manual marking of the onset and offset of P_1 is labour intensive and therefore less practical in future. For this reason, $P_{0.5}$, a time window with duration of 0.5 seconds from the onset of Phase 1, was also evaluated. The onset of Phase 1 is easier to detect and hence is more potentially amenable for automated marking. Previous studies have reported the duration of cough sounds to be within this range [192, 286]. Sound power and energy from $P_{0.5}$ was found to have a good relationship with flow and pressure, similar to that of P_1.

The correlations between cough sound power and energy and subjective cough intensity visual analogue score were strong for most subjects, demonstrating that these measures are concordant with perception of cough intensity. The likely reason for the strength of the relationship is that sound power and energy are closely correlated with cough flow and pressure, which in turn are strongly associated with subjective cough intensity (Section 6.5.7). Future studies should assess the relationship between cough sound and health related quality of life.

The factors that influence the intensity of sound are poorly understood. Differences in energy and power were found between gender and weak relationships found between sound and height and lung function. Other factors such as ethnicity, smoking and environmental exposures may also be important and warrant further investigation. A better understanding will allow the definition of normal ranges and predicted values to facilitate direct between-subjects comparisons. An alternative method for allowing between-subject comparisons is normalisation of sound measures to the values observed for each subject's maximum voluntary cough (MVC), a method used with other physiological measures such as electromyography [133, 214].

The findings in this study demonstrate that cough sound power and energy are highly repeatable. The use of automated scripts to calculate all sound parameters ensured standardisation of their calculation. Responsiveness was not evaluated in this study and this should be formally assessed in future studies. However, the ability of cough sound to discriminate differing levels of cough intensity would suggest that it has the potential to be a responsive measure.

Little difference in performance was found between sound measures derived from the free-field microphone and those derived from the contact microphone for their correlations with cough flow rate and oesophageal pressure. The free-field microphone yielded only marginally superior results. However, the performance of the free-field microphone was superior with respect to the relationship with subjective perception of cough intensity. The coefficient of variation of sound

power and energy during repeated maximum voluntary coughs was also slightly better with free-field microphones. Free-field microphones are generally more convenient and less prone to limitations that could affect contact microphones, such as quality of skin contact due to factors such as sweating and displacement.

The position of the microphone was found to have an important affect on sound power and energy, with a noted reduction with displacement of the microphone in all directions from the standardised central position. Other studies have confirmed that distance from mouth affects the intensity of cough sounds [183]. Standardisation of microphone position is therefore essential for any future qualitative studies of cough sound.

A potential application for cough sound measures of cough intensity is in the assessment over prolonged periods in an ambulatory setting. This would allow the study of any diurnal effect on cough intensity, similar to that of cough frequency [170]. A future role exists for combining cough monitoring technology to quantify cough frequency and intensity contemporaneously, permitting a more complete objective measure of global cough severity.

There are some limitations to this study. The study was restricted to voluntary cough since this permitted the evaluation of a range of different cough intensities in a systematic manner. This study should be extended to spontaneous and induced cough in future. Only isolated single coughs were studied; the findings need to be confirmed for coughs occurring within bouts. The study was limited to healthy volunteers and patients with excessive cough. Future studies in patients with weak cough are warranted to validate the findings in this population. This study was not powered to perform subgroup analyses on patients with chronic cough by aetiology of cough and therefore any potential differences would need further investigation. The facemask, which was used to house a pneumotachograph for the measurement of cough flow, could have introduced a filtering effect of cough sounds. However, any filtering effect would have been constant for each subject, and only within-subject analyses were performed. Furthermore, the performance of sound

measures from the laryngeal contact microphone, which would not have been affected by the facemask, was similar to that of the free-field microphone. Use of novel technologies such as optoelectronic or structured light plethysmography, which do not require a pneumotachograph and have been shown to correlate well with conventional spirometry, may be able to confirm these findings [288, 289]. Finally, all studies were performed in a quiet room, free from ambient noise. This was important to establish whether a relationship between sound and flow or pressure truly exists. Future ambulatory studies will need to accommodate for the effect of ambient noises.

7.7 Conclusion

Cough sound power and energy correlate strongly with physiological measures of cough intensity and subjective perception of cough intensity. Analyses from phase 1 (P_1) or 0.5 second ($P_{0.5}$) time windows yield similar results, but the latter may be preferential due to the potential for automated analysis. The use of free field microphones is recommended due to marginal superiority over contact microphones. The position of the microphone should be standardised and kept constant throughout the study period. Future studies should assess the responsiveness of cough sound measures.

8 Discussion and conclusions

8.1 Summary of key findings

The aim of this thesis was to evaluate objective measures of cough frequency and cough intensity in patients with acute and chronic cough.

Few studies have characterised cough frequency objectively in acute cough. The work within this thesis has demonstrated that in otherwise healthy subjects with acute cough, objective 24-hour cough frequency was elevated at baseline and health related quality of life was significantly impaired, similar to that of patients with chronic cough. 24-hour cough frequency reduced significantly over the 8-day study period and the minimal clinically important difference at 4 days was quantified as a 54% reduction from baseline. Minimal important differences for cough severity VAS and LCQ were also defined as 17 mm and 2.0 LCQ score changes respectively, allowing comprehensive sample size calculations for future clinical trials. This data has been used to power a multi-centre randomised placebo-controlled trial of a new antitussive drug (EudraCT number: 2013-002728-17).

The standard cough frequency monitoring duration is 24 hours and data defining 24-hour cough frequency in health and disease exists. It is a repeatable and responsive measure, but its analysis can be time consuming [146]. A shorter monitoring duration could be more convenient for patients and practical for investigators. It was hypothesised that shorter duration daytime cough frequency would be comparable to 24-hour cough frequency since most coughs occur in the daytime [119]. Shorter duration cough frequency of between 1 and 6 hours duration were all found to correlate strongly with 24-hour cough frequency. Those less than 4 hours in duration were limited by weak relationships with subjective measures of cough. 4-hour cough frequency bore a similar relationship with subjective cough severity and health related quality of life to that of 24-hour cough frequency and, importantly, was responsive to change, supporting its feasibility as a tool for assessing outcomes in chronic cough. A recent randomised controlled trial

of gabapentin for refractory cough has since cited this data to qualify the use of short duration cough frequency as an endpoint [88].

The intensity of coughs is an important determinant of global cough severity for patients with chronic cough, but most studies examining cough intensity have been conducted in healthy subjects or in patients with weak cough during experimentally induced and voluntary cough [140]. Little is known about cough intensity in patients with chronic cough and few have described it during spontaneous or pathological cough. In chapter 6, voluntary, induced and spontaneous cough in patients with chronic cough and healthy controls were studied using physiological measures of cough intensity such as oesophageal pressure, gastric pressure and cough flow. Physiological measures of cough were closely correlated with cough intensity visual analogue score, suggesting that these objective indices are important to subjective perception of cough intensity. Patients with chronic cough were found to be capable of significantly stronger maximum voluntary coughs than matched controls. Induced cough intensity also appeared greater in patients, although this did not reach statistical significance. There was no difference in expiratory muscle strength and abdominal muscle electromyography between patients and controls, but compression phase duration was increased in female patients compared to controls, suggesting that laryngeal function may be important. Cough intensity was greatest during maximum voluntary cough, and was similar between induced and spontaneous cough. Voluntary coughs were invariably preceded by an inspiration, whereas induced or spontaneous coughs predominantly contained expiratory reflexes that were present within bouts. Since cough intensity may be lower for expiratory reflexes than coughs preceded by inspiration, this could have important implications when considering the use of experimental cough models to simulate effects on spontaneous cough.

Cough sound has been suggested as a measure of cough intensity but it has not previously been validated against physiological measures of cough intensity [184]. The measurement of cough sound has the advantage of being non-invasive and ambulatory recording technology is already available. The results from chapter 7 support the feasibility of cough sound as a non-invasive measure of cough intensity.

Cough sound power and energy were highly correlated with oesophageal pressure and peak cough flow rate during voluntary cough. The strength of correlations for sound analysis from a 0.5-second time-window were similar to those from phase 1 or phases 1-3 time-windows, supporting the potential for future automated analysis. Sound power and energy were found to be highly repeatable and correlated with subjective cough intensity visual analogue score in most subjects. Further large-scale studies are now needed to define normal ranges and assess the responsiveness of these measures.

The use of sound recordings for cough monitoring can raise issues regarding privacy, especially as all sounds including private conversations would be recorded. This is an important issue and some subjects may find the risk to confidentiality by this technology too intrusive. The confidentiality of subjects is preserved as much as possible with the Leicester Cough Monitor system since the analysis is mostly automated. During the manual validation stage, the investigator is only presented with a number of one-second audio segments that the computer program has extracted from the recording, having identified these segments as containing candidate cough sounds. It is not possible to detect conversations from within these short segments. It is also important to acknowledge that there is an ethical code of conduct stipulating that investigators will not listen to an audio recording in its entirety. Any subjects undergoing such monitoring require full informed consent highlighting the ethical obligations of the investigator. The use of cough sound monitoring in all of the studies within this thesis was granted full ethics committee approval based on these reassurances. During the work for this thesis, only one subject declined participation in cough monitoring studies because of confidentiality reasons.

8.2 General limitations

Some aspects of the studies would have been improved by recruitment of a larger sample size in order to permit subgroup analysis. Larger numbers would have increased confidence in the findings of responsiveness of short duration cough frequency and provided adequate statistical power to assess the effect of

anthropometry, viral aetiology and duration of illness at recruitment on acute cough patterns. A larger sample size would also have given extra support to the finding of a strong correlation between cough sound and subjective cough severity, which was limited to the study of only 8 subjects.

Short duration and 24-hour cough frequencies were calculated from the same 24-hour recording and it is possible that patients will behave differently if they undergo 4-hour rather than 24-hour periods of monitoring. This should be addressed with prospective studies conducting short duration and 24-hour recordings separately. Cough intensity was not evaluated in tandem with cough frequency monitoring in the acute or chronic cough studies. Validated tools for assessing cough intensity in the ambulatory setting are not available but the promising role for cough sound as a non-invasive measure may facilitate this in future.

Lung volumes prior to cough were not measured during cough intensity studies, although inspired and expired lung volumes were calculated for each cough manoeuvre. Cough sounds may have been affected by a filtering effect introduced by the use of a mask to house the pneumotachograph. New technologies such as optoelectronic plethysmography may be useful for quantifying lung volumes and may be useful in future studies comparing sound with flow since this negates the need for a mask, thereby avoiding the risk of introducing sound filtering effects. The compression phase duration of cough was derived from interrogation of the respiratory flow trace, a recognised method, but laryngeal activity was not directly assessed.

Finally, the cough sound studies were performed in a quiet room free from ambient noise in order to establish the relationship between sound and physiological measures in the most optimal environment. Future ambulatory studies will need to accommodate for the effect of ambient noises.

8.3 Areas for ongoing research

A larger scale study in acute cough controlling for viral aetiology and duration of illness at recruitment would be of interest to investigate the factors that may

influence the rate of change in cough frequency. The responsiveness of short duration cough frequency should be assessed. This measure may be particularly suited to rapidly changing conditions, such as acute cough, and could be evaluated in this population.

Further detailed study of the compression phase duration is warranted to evaluate its role in the mechanism for increased cough intensity in patients with chronic cough compared to healthy controls. These studies should include direct assessment of laryngeal function and activity, for example with direct video laryngoscopy or laryngeal EMG. Larger scale studies that are powered to compare the intensity of expiratory reflexes and coughs preceded by an inspiration in spontaneous cough are also needed. The potential for cough sound as a measure of cough intensity is another exciting area for further research. The work described within this thesis has demonstrated a strong relationship between cough sound and physiological cough intensity, but the study should now be extended to spontaneous cough to identify whether the relationships remain during non-experimental cough. Furthermore, cough sound in subjects with weak cough should be prospectively studied to determine its potential for assessing ineffective cough. In addition, the responsiveness of sound power and energy should be evaluated to assess whether these measures may be useful in clinical practice.

Lastly, there is now an opportunity to consider the development of a composite outcome score which combines objective cough frequency and cough intensity with subjective cough scores for a truly comprehensive measure of global cough severity that is relevant to our patients.

9 References

1. Chaudri MB, Liu C, Hubbard R, Jefferson D, Kinnear WJ. Relationship between supramaximal flow during cough and mortality in motor neurone disease. *Eur Respir J* 2002: 19(3): 434-438.
2. Smith Hammond CA, Goldstein LB, Zajac DJ, Gray L, Davenport PW, Bolser DC. Assessment of aspiration risk in stroke patients with quantification of voluntary cough. *Neurology* 2001: 56(4): 502-506.
3. Fontana GA, Pantaleo T, Lavorini F, Benvenuti F, Gangemi S. Defective motor control of coughing in Parkinson's disease. *Am J Respir Crit Care Med* 1998: 158(2): 458-464.
4. Ebihara S, Saito H, Kanda A, Nakajoh M, Takahashi H, Arai H, Sasaki H. Impaired efficacy of cough in patients with Parkinson disease. *Chest* 2003: 124(3): 1009-1015.
5. O'Connell F, Thomas VE, Studham JM, Pride NB, Fuller RW. Capsaicin cough sensitivity increases during upper respiratory infection. *Respir Med* 1996: 90(5): 279-286.
6. Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. *Lung* 2008: 186 Suppl 1: S55-58.
7. Raj AA, Birring SS. Clinical assessment of chronic cough severity. *Pulm Pharmacol Ther* 2007: 20(4): 334-337.
8. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of Depressive Symptoms Among Patients With Chronic Cough*. *Chest* 2006: 130(6): 1839-1843.
9. French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. *Arch Intern Med* 1998: 158(15): 1657-1661.
10. Kuzniar TJ, Morgenthaler TI, Afessa B, Lim KG. Chronic cough from the patient's perspective. *Mayo Clin Proc* 2007: 82(1): 56-60.
11. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003: 58(4): 339-343.
12. French CT, Irwin RS, Fletcher KE, Adams TM. Evaluation of a Cough-Specific Quality-of-Life Questionnaire*. *Chest* 2002: 121(4): 1123-1131.
13. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. *Lancet* 2008: 371(9621): 1364-1374.
14. Morice AH. Epidemiology of cough. *Pulm Pharmacol Ther* 2002: 15(3): 253-259.
15. Propietary Association of Great Britain (PAGB). Annual Review 2012. London: Propietary Association of Great Britain. 2012:1-24.
16. Morice AH, McGarvey L, Pavord I. Recommendations for the management of cough in adults. *Thorax* 2006: 61 Suppl 1: i1-24.
17. Johnston SL, Holgate ST. Epidemiology of viral respiratory tract infections. *In:* Myint S, Taylor-Robinson D, eds. Viral and other infections infections of the human respiratory tract. Chapman & Hall, London, 1996.
18. Ford AC, Forman D, Moayyedi P, Morice AH. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax* 2006: 61(11): 975-979.

19. Irwin RS. Primary Care: The Diagnosis and Treatment of Cough. *N Engl J Med* 2000: 343(23): 1715-1721.
20. Dicpinigaitis PV, Colice GL, Goolsby MJ, Rogg GI, Spector SL, Winther B. Acute cough: a diagnostic and therapeutic challenge. *Cough (London, England)* 2009: 5: 11.
21. Fendrick A, Monto AS, Nightengale B, Sarnes M. THe economic burden of non–influenza-related viral respiratory tract infection in the united states. *Arch Intern Med* 2003: 163(4): 487-494.
22. Dicpinigaitis PV, Colice GL, Goolsby MJ, Rogg GI, Spector SL, Winther B. Acute cough: a diagnostic and therapeutic challenge. *Cough* 2009: 5: 11.
23. Abdullah H, Heaney LG, Cosby SL, McGarvey LP. Rhinovirus upregulates transient receptor potential channels in a human neuronal cell line: implications for respiratory virus-induced cough reflex sensitivity. *Thorax* 2013.
24. Boujaoude ZC, Pratter MR. Clinical approach to acute cough. *Lung* 2010: 188 Suppl 1: S41-46.
25. Smith S, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database of Systematic Reviews* 2008: Issue 1. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub3.
26. Eccles R. Importance of placebo effect in cough clinical trials. *Lung* 2010: 188 Suppl 1: S53-61.
27. Braman SS. Postinfectious cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006: 129(1 Suppl): 138S-146S.
28. Ponsioen BP, Hop WCJ, Vermue NA, Dekhuijzen PNR, Bohnen AM. Efficacy of fluticasone on cough: a randomised controlled trial. *Eur Respir J* 2005: 25(1): 147-152.
29. van Hoek AJ, Campbell H, Amirthalingam G, Andrews N, Miller E. The number of deaths among infants under one year of age in England with pertussis: results of a capture/recapture analysis for the period 2001 to 2011. *Eurosurveillance* 2013: 18(9).
30. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981: 123(4 Pt 1): 413-417.
31. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990: 141(3): 640-647.
32. Poe RH, Harder RV, Israel RH, Kallay MC. Chronic persistent cough. Experience in diagnosis and outcome using an anatomic diagnostic protocol. *Chest* 1989: 95(4): 723-728.
33. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Chest* 1995: 108(4): 991-997.

34. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med* 1996: 156(9): 997-1003.
35. McGarvey LPA, Heaney LG, Lawson JT, Johnston BT, Scally CM, Ennis M, Shepherd DRT, MacMahon J. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax* 1998: 53(9): 738-743.
36. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med* 1999: 160(2): 406-410.
37. Birring SS, Passant C, Patel RB, Prudon B, Murty GE, Pavord ID. Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough. *Eur Respir J* 2004: 23(2): 199-201.
38. Niimi A, Torrego A, Nicholson AG, Cosio BG, Oates TB, Chung KF. Nature of airway inflammation and remodeling in chronic cough. *J Allergy Clin Immunol* 2005: 116(3): 565-570.
39. Kastelik JA, Aziz I, Ojoo JC, Thompson RH, Redington AE, Morice AH. Investigation and management of chronic cough using a probability-based algorithm. *Eur Respir J* 2005: 25(2): 235-243.
40. Fujimura M, Abo M, Ogawa H, Nishi K, Kibe Y, Hirose T, Nakatsumi Y, Iwasa K. Importance of atopic cough, cough variant asthma and sinobronchial syndrome as causes of chronic cough in the Hokuriku area of Japan. *Respirology* 2005: 10(2): 201-207.
41. Shirahata K, Fujimoto K, Arioka H, Shouda R, Kudo K, Ikeda S-I. Prevalence and clinical features of cough variant asthma in a general internal medicine outpatient clinic in Japan. *Respirology* 2005: 10(3): 354-358.
42. Palombini BC, Villanova CAC, Araújo E, Gastal OL, Alt DC, Stolz DP, Palombini CO. A Pathogenic Triad in Chronic Cough*. *Chest* 1999: 116(2): 279-284.
43. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979: 300(12): 633-637.
44. Glauser FL. Variant asthma. *Ann Allergy* 1972: 30(8): 457-459.
45. Pavord ID, Chung KF. Management of chronic cough. *Lancet* 2008: 371(9621): 1375-1384.
46. Niimi A, Amitani R, Suzuki K, Tanaka E, Murayama T, Kuze F. Eosinophilic inflammation in cough variant asthma. *Eur Respir J* 1998: 11(5): 1064-1069.
47. Niimi A, Matsumoto H, Minakuchi M, Kitaichi M, Amitani R. Airway remodelling in cough-variant asthma. *Lancet* 2000: 356(9229): 564-565.
48. Prudon B, Birring SS, Vara DD, Hall AP, Thompson JP, Pavord ID. Cough and glottic-stop reflex sensitivity in health and disease. *Chest* 2005: 127(2): 550-557.
49. Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. *Chest* 2002: 121(4): 1051-1057.
50. Cockcroft DW, Jokic R, Marciniuk DD, Fitzpatrick MF. The current dilemma with spirometric inclusion criteria for asthma drug trials. *Annals of Allergy, Asthma, & Immunology* 1997: 79(3): 226-228.

51. Chatkin JM, Ansarin K, Silkoff PE, McClean P, Gutierrez C, Zamel N, Chapman KR. Exhaled nitric oxide as a noninvasive assessment of chronic cough. *Am J Respir Crit Care Med* 1999: 159(6): 1810-1813.
52. Birring SS. Controversies in the evaluation and management of chronic cough. *Am J Respir Crit Care Med* 2011: 183(6): 708-715.
53. Cheriyan S, Greenberger PA, Patterson R. Outcome of cough variant asthma treated with inhaled steroids. *Ann Allergy* 1994: 73(6): 478-480.
54. Millar MM, McGrath KG, Patterson R. Malignant cough equivalent asthma: definition and case reports. *Ann Allergy Asthma Immunol* 1998: 80(4): 345-351.
55. Irwin RS, French CT, Smyrnios NA, Curley FJ. Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. *Arch Intern Med* 1997: 157(17): 1981-1987.
56. Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *J Asthma* 2002: 39(4): 291-297.
57. Fujimura M, Ogawa H, Nishizawa Y, Nishi K. Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma? *Thorax* 2003: 58(1): 14-18.
58. Gibson PG, Denburg J, Dolovich J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. *Lancet* 1989: 333(8651): 1346-1348.
59. Gibson PG, Girgis-Gabardo A, Morris MM, Mattoli S, Kay JM, Dolovich J, Denburg J, Hargreave FE. Cellular characteristics of sputum from patients with asthma and chronic bronchitis. *Thorax* 1989: 44(9): 693-699.
60. Brightling CE, Ward R, Wardlaw AJ, Pavord ID. Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. *Eur Respir J* 2000: 15(4): 682-686.
61. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-Cell Infiltration of Airway Smooth Muscle in Asthma. *N Engl J Med* 2002: 346(22): 1699-1705.
62. Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. *Thorax* 2002: 57(2): 178-182.
63. Fujimura M, Ogawa H, Yasui M, Matsuda T. Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough. *Clin Exp Allergy* 2000: 30(1): 41-47.
64. Irwin RS, Rosen MJ, Braman SS. Cough: A Comprehensive Review. *Arch Intern Med* 1977: 137(9): 1186-1191.
65. Gastal OL, Castell JA, Castell DO. Frequency and Site of Gastroesophageal Reflux in Patients With Chest Symptoms. *Chest* 1994: 106(6): 1793-1796.
66. Pauwels A, Blondeau K, Dupont L, Sifrim D. Cough and gastroesophageal reflux: from the gastroenterologist end. *Pulm Pharmacol Ther* 2009: 22(2): 135-138.
67. Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. *Am J Respir Crit Care Med* 1994: 149(1): 160-167.
68. Faruqi S, Molyneux ID, Fathi H, Wright C, Thompson R, Morice AH. Chronic cough and esomeprazole: A double-blind placebo-controlled parallel study. *Respirology* 2011: 16(7): 1150-1156.

69. Shaheen NJ, Crockett SD, Bright SD, Madanick RD, Buckmire R, Couch M, Dellon ES, Galanko JA, Sharpless G, Morgan DR, Spacek MB, Heidt-Davis P, Henke D. Randomised clinical trial: high-dose acid suppression for chronic cough - a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011: 33(2): 225-234.
70. Chang AB, Lasserson TJ, Kiljander TO, Connor FL, Gaffney JT, Garske LA. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. *BMJ* 2006: 332(7532): 11-17.
71. Blondeau K, Dupont LJ, Mertens V, Tack J, Sifrim D. Improved diagnosis of gastro-oesophageal reflux in patients with unexplained chronic cough. *Aliment Pharmacol Ther* 2007: 25(6): 723-732.
72. Smith JA, Decalmer S, Kelsall A, McGuinness K, Jones H, Galloway S, Woodcock A, Houghton LA. Acoustic Cough—Reflux Associations in Chronic Cough: Potential Triggers and Mechanisms. *Gastroenterology* 2010: 139(3): 754-762.
73. Paterson WG, Murat BW. Combined ambulatory esophageal manometry and dual-probe pH-metry in evaluation of patients with chronic unexplained cough. *Digestive Diseases & Sciences* 1994: 39(5): 1117-1125.
74. Patterson N, Mainie I, Rafferty G, McGarvey L, Heaney L, Tutuian R, Castell D, Johnston BT. Nonacid reflux episodes reaching the pharynx are important factors associated with cough. *J Clin Gastroenterol* 2009: 43(5): 414-419.
75. Decalmer S, Stovold R, Houghton LA, Pearson J, Ward C, Kelsall A, Jones H, McGuinness K, Woodcock A, Smith JA. Chronic cough: Relationship between microaspiration, gastroesophageal reflux, and cough frequency. *Chest* 2012: 142(4): 958-964.
76. Ours TM, Kavuru MS, Schilz RJ, Richter JE. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999: 94(11): 3131-3138.
77. Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med* 2008: 359(16): 1700-1707.
78. Irwin RS, Baumann MH, Bolser DC, Boulet L-P, Braman SS, Brightling CE, Brown KK, Canning BJ, Chang AB, Dicpinigaitis PV, Eccles R, Glomb WB, Goldstein LB, Graham LM, Hargreave FE, Kvale PA, Lewis SZ, McCool FD, McCrory DC, Prakash UBS, Pratter MR, Rosen MJ, Schulman E, Shannon JJ, Smith Hammond C, Tarlo SM, American College of Chest P. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006: 129(1 Suppl): 1S-23S.
79. Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dicpinigaitis PV, Kastelik JA, McGarvey LP, Smith JA, Tatar M, Widdicombe J, European Respiratory S. ERS guidelines on the assessment of cough. *Eur Respir J* 2007: 29(6): 1256-1276.
80. Haque RA, Usmani OS, Barnes PJ. Chronic idiopathic cough: a discrete clinical entity? *Chest* 2005: 127(5): 1710-1713.
81. Brightling CE, Symon FA, Birring SS, Bradding P, Wardlaw AJ, Pavord ID. Comparison of airway immunopathology of eosinophilic bronchitis and asthma. *Thorax* 2003: 58(6): 528-532.

82. Birring SS, Morgan AJ, Prudon B, McKeever TM, Lewis SA, Falconer Smith JF, Robinson RJ, Britton JR, Pavord ID. Respiratory symptoms in patients with treated hypothyroidism and inflammatory bowel disease. *Thorax* 2003: 58(6): 533-536.
83. Morice A, Faruqi S, Wright C, Thompson R, Bland J. Cough Hypersensitivity Syndrome: A Distinct Clinical Entity. *Lung* 2011: 189(1): 73-79.
84. Lee KK, Birring SS. Cough. *Medicine* 2012: 40(4): 173-176.
85. Morice AH, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, Thompson R. Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007: 175(4): 312-315.
86. Jeyakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. *Laryngoscope* 2006: 116(12): 2108-2112.
87. Mintz S, Lee JK. Gabapentin in the treatment of intractable idiopathic chronic cough: case reports. *Am J Med* 2006: 119(5): e13-15.
88. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet* 2012: 380(9853): 1583-1589.
89. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax* 2006: 61(12): 1065-1069.
90. Patel AS, Watkin G, Willig B, Mutalithas K, Bellas H, Garrod R, Pavord ID, Birring SS. Improvement in health status following cough-suppression physiotherapy for patients with chronic cough. *Chronic Respir Dis* 2011: 8(4): 253-258.
91. Widdicombe JG. Afferent receptors in the airways and cough. *Respir Physiol* 1998: 114(1): 5-15.
92. Canning BJ. Functional implications of the multiple afferent pathways regulating cough. *Pulm Pharmacol Ther* 2011: 24(3): 295-299.
93. Belvisi MG, Bolser DC. Summary: Animal Models for Cough. *Pulm Pharmacol Ther* 2002: 15(3): 249-250.
94. Lewis CA, Ambrose C, Banner K, Battram C, Butler K, Giddings J, Mok J, Nasra J, Winny C, Poll C. Animal models of cough: Literature review and presentation of a novel cigarette smoke-enhanced cough model in the guinea-pig. *Pulm Pharmacol Ther* 2007: 20(4): 325-333.
95. O'Connell F, Thomas VE, Pride NB, Fuller RW. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. *Am J Respir Crit Care Med* 1994: 150(2): 374-380.
96. Vertigan AE, Gibson PG. Chronic refractory cough as a sensory neuropathy: evidence from a reinterpretation of cough triggers. *J Voice* 2011: 25(5): 596-601.
97. Canning BJ, Mori N, Mazzone SB. Vagal afferent nerves regulating the cough reflex. *Respiratory physiology & neurobiology* 2006: 152(3): 223-242.
98. Adcock J J. TRPV1 receptors in sensitisation of cough and pain reflexes. *Pulm Pharmacol Ther* 2009: 22(2): 65-70.
99. Mezey É, Tóth ZE, Cortright DN, Arzubi MK, Krause JE, Elde R, Guo A, Blumberg PM, Szallasi A. Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human. *Proceedings of the National Academy of Sciences* 2000: 97(7): 3655-3660.

100. Guo A, Vulchanova L, Wang J, Li X, Elde R. Immunocytochemical localization of the vanilloid receptor 1 (VR1): relationship to neuropeptides, the P2X3 purinoceptor and IB4 binding sites. *Eur J Neurosci* 1999: 11(3): 946-958.
101. Patterson L, Zheng H, Ward S, Berthoud H-R. Vanilloid receptor (VR1) expression in vagal afferent neurons innervating the gastrointestinal tract. *Cell Tissue Res* 2003: 311(3): 277-287.
102. Taylor-Clark TE, Kollarik M, MacGlashan DW, Undem BJ. Nasal sensory nerve populations responding to histamine and capsaicin. *J Allergy Clin Immunol* 2005: 116(6): 1282-1288.
103. Morice AH, Geppetti P. Cough. 5: The type 1 vanilloid receptor: a sensory receptor for cough. *Thorax* 2004: 59(3): 257-258.
104. Groneberg DA, Niimi A, Dinh QT, Cosio B, Hew M, Fischer A, Chung KF. Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. *Am J Respir Crit Care Med* 2004: 170(12): 1276-1280.
105. Belvisi MG, Geppetti P. Cough. 7: Current and future drugs for the treatment of chronic cough. *Thorax* 2004: 59(5): 438-440.
106. Gibson PG, Ryan NM. Cough pharmacotherapy: current and future status. *Expert Opinion on Pharmacotherapy* 2011: 12(11): 1745-1755.
107. Widdicombe J, Fontana G. Cough: what's in a name? *Eur Respir J* 2006: 28(1): 10-15.
108. Hill AV. The mechanics of voluntary muscle. *Lancet* 1951: 2(6691): 947-951.
109. McCool FD. Global Physiology and Pathophysiology of Cough. *Chest* 2006: 129(1 suppl): 48S-53S.
110. Ryschon TW, Fowler MD, Wysong RE, Anthony A, Balaban RS. Efficiency of human skeletal muscle in vivo: comparison of isometric, concentric, and eccentric muscle action. *Journal of Applied Physiology* 1997: 83(3): 867-874.
111. Polkey MI, Lyall RA, Green M, Nigel Leigh P, Moxham J. Expiratory muscle function in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 1998: 158(3): 734-741.
112. Bennett WD, Zeman KL. Effect of enhanced supramaximal flows on cough clearance. *J Appl Physiol* 1994: 77(4): 1577-1583.
113. Ross BB, Gramiak R, Rahn H. Physical dynamics of the cough mechanism. *J Appl Physiol* 1955: 8(3): 264-268.
114. Szeinberg A, Tabachnik E, Rashed N, McLaughlin FJ, England S, Bryan CA, Levison H. Cough capacity in patients with muscular dystrophy. *Chest* 1988: 94(6): 1232-1235.
115. Korpas J, Sadlonova J, Vrabec M. Analysis of the cough sound: an overview. *Pulm Pharmacol* 1996: 9(5-6): 261-268.
116. Hutchings HA, Morris S, Eccles R, Jawad MS. Voluntary suppression of cough induced by inhalation of capsaicin in healthy volunteers. *Respir Med* 1993: 87(5): 379-382.
117. Lee PCL, Cotterill-Jones C, Eccles R. Voluntary control of cough. *Pulmonary Pharmacology & Therapeutics* 2002: 15(3): 317-320.
118. Davenport PW, Vovk A, Duke RK, Bolser DC, Robertson E. The urge-to-cough and cough motor response modulation by the central effects of nicotine. *Pulmonary Pharmacology & Therapeutics* 2009: 22(2): 82-89.

119. Hsu JY, Stone RA, Logan-Sinclair RB, Worsdell M, Busst CM, Chung KF. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. *Eur Respir J* 1994: 7(7): 1246-1253.
120. Kelsall A, Decalmer S, Webster D, Brown N, McGuinness K, Woodcock A, Smith J. How to quantify coughing: correlations with quality of life in chronic cough. *Eur Respir J* 2008: 32(1): 175-179.
121. Wang HD, Nakagawa T, Sekizawa K, Kamanaka M, Sasaki H. Cough reflex in the night. *Chest* 1998: 114(5): 1496-1497.
122. Eccles R. Mechanisms of the placebo effect of sweet cough syrups. *Respiratory physiology & neurobiology* 2006: 152(3): 340-348.
123. Fontana GA, Widdicombe J. What is cough and what should be measured? *Pulm Pharmacol Ther* 2007: 20(4): 307-312.
124. Nishino T, Tagaito Y, Isono S. Cough and other reflexes on irritation of airway mucosa in man. *Pulm Pharmacol* 1996: 9(5-6): 285-292.
125. Smith JA, Aliverti A, Quaranta M, McGuinness K, Kelsall A, Earis J, Calverley PM. Chest wall dynamics during voluntary and induced cough in healthy volunteers. *J Physiol (Lond)* 2012: 590(Pt 3): 563-574.
126. Poliacek I, Stransky A, Jakus J, Barani H, Tomori Z, Halasova E. Activity of the laryngeal abductor and adductor muscles during cough, expiration and aspiration reflexes in cats. *Physiol Res* 2003: 52(6): 749-762.
127. Tatar M, Hanacek J, Widdicombe J. The expiration reflex from the trachea and bronchi. *Eur Respir J* 2008: 31(2): 385-390.
128. Strohl KP, Mead J, Banzett RB, Loring SH, Kosch PC. Regional differences in abdominal muscle activity during various maneuvers in humans. *J Appl Physiol* 1981: 51(6): 1471-1476.
129. Goldman JM, Lehr RP, Millar AB, Silver JR. An electromyographic study of the abdominal muscles during postural and respiratory manoeuvres. *J Neurol Neurosurg Psychiatry* 1987: 50(7): 866-869.
130. Fontana GA, Lavorini F. Cough motor mechanisms. *Respiratory physiology & neurobiology* 2006: 152(3): 266-281.
131. Estenne M, De Troyer A. Cough in tetraplegic subjects: an active process. *Ann Intern Med* 1990: 112(1): 22-28.
132. Fujiwara T, Hara Y, Chino N. Expiratory function in complete tetraplegics: study of spirometry, maximal expiratory pressure, and muscle activity of pectoralis major and latissimus dorsi muscles. *American Journal of Physical Medicine and Rehabilitation* 1999: 78(5): 464-469.
133. Lasserson D, Mills K, Arunachalam R, Polkey M, Moxham J, Kalra L. Differences in motor activation of voluntary and reflex cough in humans. *Thorax* 2006: 61(8): 699-705.
134. Poletto CJ, Verdun LP, Strominger R, Ludlow CL. Correspondence between laryngeal vocal fold movement and muscle activity during speech and nonspeech gestures. *J Appl Physiol* 2004: 97(3): 858-866.
135. Addington WR, Stephens RE, Phelipa MM, Widdicombe JG, Ockey RR. Intra-abdominal pressures during voluntary and reflex cough. *Cough* 2008: 4: 2.

136. Stephens RE, Addington WR, Miller SP, Anderson JW. Videofluoroscopy of the diaphragm during voluntary and reflex cough in humans. *Am J Phys Med Rehabil* 2003: 82(5): 384.
137. Vernon M, Leidy NK, Nacson A, Nelsen L. Measuring cough severity: Perspectives from the literature and from patients with chronic cough. *Cough (London, England)* 2009: 5: 5.
138. Everett CF, Kastelik JA, Thompson RH, Morice AH. Chronic persistent cough in the community: a questionnaire survey. *Cough* 2007: 3: 5.
139. McGarvey LPA. Patterns of cough in the clinic. *Pulm Pharmacol Ther* 2011: 24(3): 300-303.
140. Vernon M, Leidy NK, Nacson A, Nelsen L. Measuring cough severity: Perspectives from the literature and from patients with chronic cough. *Cough* 2009: 5: 5.
141. Brunekreef B, Groot B, Rijcken B, Hoek G, Steenbekkers A, de Boer A. Reproducibility of childhood respiratory symptom questions. *Eur Respir J* 1992: 5(8): 930-935.
142. Hamutcu R, Francis J, Karakoc F, Bush A. Objective monitoring of cough in children with cystic fibrosis. *Pediatr Pulmonol* 2002: 34(5): 331-335.
143. Chang AB, Newman RG, Carlin JB, Phelan PD, Robertson CF. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. *Eur Respir J* 1998: 11(2): 462-466.
144. Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. *Pediatr Pulmonol* 1993: 15(4): 209-211.
145. Brightling CE, Monterio W, Green RH, Parker D, Morgan MD, Wardlaw AJ, Pavord D. Induced sputum and other outcome measures in chronic obstructive pulmonary disease: safety and repeatability. *Respiratory Medicine* 2001: 95(12): 999-1002.
146. Faruqi S, Thompson R, Wright C, Sheedy W, Morice AH. Quantifying chronic cough: objective versus subjective measurements. *Respirology* 2011: 16(2): 314-320.
147. Decalmer SC, Webster D, Kelsall AA, McGuinness K, Woodcock AA, Smith JA. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? *Thorax* 2007: 62(4): 329-334.
148. Yousaf N, Lee KK, Jayaraman B, Pavord ID, Birring SS. The assessment of quality of life in acute cough with the Leicester Cough Questionnaire (LCQ-acute). *Cough (London, England)* 2011: 7(1): 4.
149. Raj AA, Pavord DI, Birring SS. Clinical cough IV:what is the minimal important difference for the Leicester Cough Questionnaire? *Handb* 2009(187): 311-320.
150. Berkhof FF, Boom LN, ten Hertog NE, Uil SM, Kerstjens HA, van den Berg JW. The validity and precision of the Leicester Cough Questionnaire in COPD patients with chronic cough. *Health and Quality of Life Outcomes* 2012: 10: 4.
151. Key AL, Holt K, Hamilton A, Smith JA, Earis JE. Objective cough frequency in Idiopathic Pulmonary Fibrosis. *Cough* 2010: 6: 4.
152. Murray MP. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009: 34(1): 125-131.

153. Marsden PA, Smith JA, Kelsall AA, Owen E, Naylor JR, Webster D, Sumner H, Alam U, McGuinness K, Woodcock AA. A comparison of objective and subjective measures of cough in asthma. *J Allergy Clin Immunol* 2008: 122(5): 903-907.
154. Fathi H, Moon T, Donaldson J, Jackson W, Sedman P, Morice AH. Cough in adult cystic fibrosis: diagnosis and response to fundoplication. *Cough* 2009: 5: 1.
155. Polley L. Impact of cough across different chronic respiratory diseases - Comparison of two cough-specific health-related quality of life questionnaires. *Chest* 2008: 134(2): 295-302.
156. Baiardini I, Braido F, Fassio O, Tarantini F, Pasquali M, Tarchino F, Berlendis A, Canonica GW. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. *Allergy* 2005: 60(4): 482-488.
157. Braido F, Baiardini I, Tarantini F, Fassio O, Balestracci S, Pasquali M, Tarchino F, Canonica GW. Chronic cough and QoL in allergic and respiratory diseases measured by a new specific validated tool-CCIQ. *J Investig Allergol Clin Immunol* 2006: 16(2): 110-116.
158. Coyle MA, Keenan DB, Henderson LS, Watkins ML, Haumann BK, Mayleben DW, Wilson MG. Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. *Cough* 2005: 1: 3.
159. Smith J, Owen E, Earis J, Woodcock A. Cough in COPD. *Chest* 2006: 130(2): 379-385.
160. Gravenstein JS, Devloo RA, Beecher HK. Effect of antitussive agents on experimental and pathological cough in man. *J Appl Physiol* 1954: 7(2): 119-139.
161. Woolf CR, Rosenberg A. Objective Assessment of Cough Suppressants under Clinical Conditions Using a Tape Recorder System. *Thorax* 1964: 19: 125-130.
162. Reece CA, Cherry AC, Jr., Reece AT, Hatcher TB, Diehl AM. Tape recorder for evaluation of coughs in children. *Am J Dis Child* 1966: 112(2): 124-128.
163. Ruhle KH, Graber U, Matthys H. [Comparison of the antitussive effect of two different drugs regarding frequency and strength of cough attacks (author's transl)]. *Med Klin* 1977: 72(47): 2019-2023.
164. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983: 11(2): 92-100.
165. Ruhle KH, Criscuolo D, Dieterich HA, Kohler D, Riedel G. Objective evaluation of dextromethorphan and glaucine as antitussive agents. *Br J Clin Pharmacol* 1984: 17(5): 521-524.
166. Salmi T, Sovijarvi AR, Brander P, Piirila P. Long-term recording and automatic analysis of cough using filtered acoustic signals and movements on static charge sensitive bed. *Chest* 1988: 94(5): 970-975.
167. Chang A, Newman R, Phelan P, Robertson C. A new use for an old Holter monitor: an ambulatory cough meter. *Eur Respir J* 1997: 10(7): 1637-1639.
168. Paul IM, Wai K, Jewell SJ, Shaffer ML, Varadan VV. Evaluation of a new self-contained, ambulatory, objective cough monitor. *Cough (London, England)* 2006: 2: 7.
169. Birring SS, Mann VM, Matos S, Yousaf N, Wood C, Fleming T, Evans DH, Morice AH, Pavord ID. The Leicester Cough Monitor: a semi-automated, semi-validated cough detection system? *Eur Respir J* 2008: 32(2): 530-531;author reply.

170. Lee KK, Savani A, Matos S, Evans DH, Pavord ID, Birring SS. Four-Hour Cough Frequency Monitoring in Chronic Cough. *Chest* 2012: 142(5): 1237-1243.
171. Matos S, Birring SS, Pavord ID, Evans DH. Detection of cough signals in continuous audio recordings using hidden Markov models. *IEEE Trans Biomed Eng* 2006: 53(6): 1078-1083.
172. Matos S, Birring SS, Pavord ID, Evans DH. An automated system for 24-h monitoring of cough frequency: the leicester cough monitor. *IEEE Trans Biomed Eng* 2007: 54(8): 1472-1479.
173. Birring SS, Fleming T, Matos S, Raj AA, Evans DH, Pavord ID. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. *Eur Respir J* 2008: 31(5): 1013-1018.
174. McGuinness K, Morice A, Woodcock A, Smith J. The Leicester Cough Monitor: a semi-automated, semi-validated cough detection system? *Eur Respir J* 2008: 32(2): 529-530.
175. Yousaf N, Monteiro W, Matos S, Birring SS, Pavord ID. Cough frequency in health and disease. *Eur Respir J* 2013: 41(1): 241-243.
176. Yousaf N, Monteiro W, Parker D, Matos S, Birring S, Pavord ID. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. *Thorax* 2010: 65(12): 1107-1110.
177. Kelsall A, Houghton LA, Jones H, Decalmer S, McGuinness K, Smith JA. A novel approach to studying the relationship between subjective and objective measures of cough. *Chest* 2011: 139(3): 569-575.
178. Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. *Cough* 2006: 2: 6.
179. Barry SJ, Dane AD, Morice AH, Walmsley AD. The automatic recognition and counting of cough. *Cough* 2006: 2: 8.
180. Munyard P, Busst C, Logan-Sinclair R, Bush A. A new device for ambulatory cough recording. *Pediatr Pulmonol* 1994: 18(3): 178-186.
181. Corrigan DL, Paton JY. Pilot study of objective cough monitoring in infants. *Pediatr Pulmonol* 2003: 35(5): 350-357.
182. Chang AB, Phelan PD, Robertson CF, Roberts RG, Sawyer SM. Relation between measurements of cough severity. *Arch Dis Child* 2003: 88(1): 57-60.
183. Subburaj S, Parvez L, Rajagopalan TG. Methods of recording and analysing cough sounds. *Pulm Pharmacol* 1996: 9(5-6): 269-279.
184. Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. *Chest* 2001: 120(4): 1121-1128.
185. Paul IM, Wai K, Jewell SJ, Shaffer ML, Varadan VV. Evaluation of a new self-contained, ambulatory, objective cough monitor. *Cough* 2006: 2: 7.
186. Barry SJ, Dane AD, Morice AH, Walmsley AD. The automatic recognition and counting of cough. *Cough (London, England)* 2006: 2: 8.
187. Thorpe C, Toop L, Dawson K. Towards a quantitative description of asthmatic cough sounds. *Eur Respir J* 1992: 5(6): 685-692.

188. Murata A, Taniguchi Y, Hashimoto Y, Kaneko Y, Takasaki Y, Kudoh S. Discrimination of productive and non-productive cough by sound analysis. *Intern Med* 1998: 37(9): 732-735.
189. Doherty MJ, Wang LJ, Donague S, Pearson MG, Downs P, Stoneman SA, Earis JE. The acoustic properties of capsaicin-induced cough in healthy subjects. *Eur Respir J* 1997: 10(1): 202-207.
190. Korpáš J, Vrabec M. Single, double and multi cough sound differentiation. *Acta Physiol Hung* 2005: 92(3): 203-209.
191. Piirila P, Sovijarvi AR. Objective assessment of cough. *Eur Respir J* 1995: 8(11): 1949-1956.
192. Debreczeni LA, Korpas J, Salat D. Spectral analysis of cough sounds recorded with and without a nose clip. *Bull Eur Physiopathol Respir* 1987: 23 Suppl 10: 57s-61s.
193. Kelemen SA, Cseri T, Marozsan I. Information obtained from tussigrams and the possibilities of their application in medical practice. *Bull Eur Physiopathol Respir* 1987: 23 Suppl 10: 51s-56s.
194. Piirila P, Sovijarvi AR. Differences in acoustic and dynamic characteristics of spontaneous cough in pulmonary diseases. *Chest* 1989: 96(1): 46-53.
195. Korpas J, Korpasova-Sadlonova J. Phonography of voluntary cough under pathological conditions. *Bratisl Lek Listy* 1982: 77(5): 534-543.
196. Abaza AA, Day JB, Reynolds JS, Mahmoud AM, Goldsmith WT, McKinney WG, Petsonk EL, Frazer DG. Classification of voluntary cough sound and airflow patterns for detecting abnormal pulmonary function. *Cough* 2009: 5: 8.
197. Smith JA, Ashurst HL, Jack S, Woodcock AA, Earis JE. The description of cough sounds by healthcare professionals. *Cough* 2006: 2: 1.
198. Birring SS, Matos S, Patel RB, Prudon B, Evans DH, Pavord ID. Cough frequency, cough sensitivity and health status in patients with chronic cough. *Respir Med* 2006: 100(6): 1105-1109.
199. Sumner H, Woodcock A, Kolsum U, Dockry R, Lazaar AL, Singh D, Vestbo J, Smith JA. Predictors of Objective Cough Frequency in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2013: 187(9): 943-949.
200. Smith JA, Owen EC, Jones AM, Dodd ME, Webb AK, Woodcock A. Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis. *Thorax* 2006: 61(5): 425-429.
201. Hay AD, Wilson A, Fahey T, Peters TJ. The duration of acute cough in pre-school children presenting to primary care: a prospective cohort study. *Fam Pract* 2003: 20(6): 696-705.
202. Jones BF, Stewart MA. Duration of cough in acute upper respiratory tract infections. *Aust Fam Physician* 2002: 31(10): 971-973.
203. Lee PC, Jawad MS, Hull JD, West WH, Shaw K, Eccles R. The antitussive effect of placebo treatment on cough associated with acute upper respiratory infection. *Psychosom Med* 2005: 67(2): 314-317.
204. Sunger K, Powley W, Kelsall A, Sumner H, Murdoch R, Smith JA. Objective measurement of cough in otherwise healthy volunteers with acute cough. *Eur Respir J* 2013: 41(2): 277-284.

205. Ward K, Seymour J, Steier J, Jolley CJ, Polkey MI, Kalra L, Moxham J. Acute ischaemic hemispheric stroke is associated with impairment of reflex in addition to voluntary cough. *Eur Respir J* 2010: 36(6): 1383-1390.
206. Fontana GA, Pantaleo T, Lavorini F, Mutolo D, Polli G, Pistolesi M. Coughing in laryngectomized patients. *Am J Respir Crit Care Med* 1999: 160(5 Pt 1): 1578-1584.
207. Man WD-C, Kyroussis D, Fleming TA, Chetta A, Harraf F, Mustfa N, Rafferty GF, Polkey MI, Moxham J. Cough Gastric Pressure and Maximum Expiratory Mouth Pressure in Humans. *Am J Respir Crit Care Med* 2003: 168(6): 714-717.
208. Dicpinigaitis PV. Experimentally induced cough. *Pulm Pharmacol Ther* 2007: 20(4): 319-324.
209. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. *J Pharm Pharmacol* 1997: 49(10): 1045-1049.
210. Dicpinigaitis P, Dobkin J, Rauf K. Comparison of the Antitussive Effects of Codeine and the GABA-Agonist Baclofen. *Clin Drug Invest* 1997: 14(4): 326-329.
211. Cox ID, Wallis PJ, Apps MC, Hughes DT, Empey DW, Osman RC, Burke CA. An electromyographic method of objectively assessing cough intensity and use of the method to assess effects of codeine on the dose-response curve to citric acid. *Br J Clin Pharmacol* 1984: 18(3): 377-382.
212. Chellini E, Magni C, Lavorini F, Rucci L, Fontana G. Motor features of voluntary cough following partial laryngectomy for glottal carcinoma. *Bratisl Lek Listy* 2011: 112(3): 115-119.
213. Davenport PW, Bolser DC, Vickroy T, Berry RB, Martin AD, Hey JA, Danzig M. The effect of codeine on the Urge-to-Cough response to inhaled capsaicin. *Pulm Pharmacol Ther* 2007: 20(4): 338-346.
214. Fontana GA, Pantaleo T, Lavorini F, Boddi V, Panuccio P. A noninvasive electromyographic study on threshold and intensity of cough in humans. *Eur Respir J* 1997: 10(5): 983-989.
215. Fontana GA, Pantaleo T, Lavorini F, Maluccio NM, Mutolo D, Pistolesi M. Repeatability of cough-related variables during fog challenges at threshold and suprathreshold stimulus intensity in humans. *Eur Respir J* 1999: 13(6): 1447-1450.
216. Kim J, Davenport P, Sapienza C. Effect of expiratory muscle strength training on elderly cough function. *Arch Gerontol Geriatr* 2009: 48(3): 361-366.
217. Kyroussis D, Polkey MI, Mills GH, Hughes PD, Moxham J, Green M. Simulation of cough in man by magnetic stimulation of the thoracic nerve roots. *Am J Respir Crit Care Med* 1997k: 156(5): 1696-1699.
218. Lavietes M, Smeltzer S, Cook S, Modak R, Smaldone G. Airway dynamics, oesophageal pressure and cough. *Eur Respir J* 1998: 11(1): 156-161.
219. Lavorini F, Pantaleo T, Geri P, Mutolo D, Pistolesi M, Fontana GA. Cough and ventilatory adjustments evoked by aerosolised capsaicin and distilled water (fog) in man. *Respiratory physiology & neurobiology* 2007: 156(3): 331-339.
220. Lavorini F, Fontana GA, Pantaleo T, Geri P, Piumelli R, Pistolesi M, Widdicombe J. Fog-induced cough with impaired respiratory sensation in congenital central hypoventilation syndrome. *Am J Respir Crit Care Med* 2007: 176(8): 825-832.

221. Man WD, Hopkinson NS, Harraf F, Nikoletou D, Polkey MI, Moxham J. Abdominal muscle and quadriceps strength in chronic obstructive pulmonary disease. *Thorax* 2005: 60(9): 718-722.
222. Murty GE, Smith MC, Lancaster P. Cough intensity in the laryngectomee. *Clinical Otolaryngology & Allied Sciences* 1991: 16(1): 25-28.
223. Pitts T, Bolser D, Rosenbek J, Troche M, Sapienza C. Voluntary Cough Production and Swallow Dysfunction in Parkinson's Disease. *Dysphagia* 2008: 23(3): 297-301.
224. Pitts T, Bolser D, Rosenbek J, Troche M, Okun MS, Sapienza C. Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson disease. *Chest* 2009: 135(5): 1301-1308.
225. Reilly CC, Ward K, Jolley CJ, Frank LA, Elston C, Moxham J, Rafferty GF. Effect of endurance exercise on respiratory muscle function in patients with cystic fibrosis. *Respiratory physiology & neurobiology* 2012: 180(2–3): 316-322.
226. Steier J, Kaul S, Seymour J, Jolley C, Rafferty G, Man W, Luo YM, Roughton M, Polkey MI, Moxham J. The value of multiple tests of respiratory muscle strength. *Thorax* 2007: 62(11): 975-980.
227. Smith J, Woodcock A. New developments in the objective assessment of cough. *Lung* 2008: 186 Suppl 1: S48-54.
228. Desmedt JE, Godaux E. Ballistic contractions in man: characteristic recruitment pattern of single motor units of the tibialis anterior muscle. *J Physiol (Lond)* 1977: 264(3): 673-693.
229. Burbank DP, Webster JG. Reducing skin potential motion artefact by skin abrasion. *Med Biol Eng Comput* 1978: 16(1): 31-38.
230. Lavorini F, Fontana GA, Chellini E, Magni C, Pistolesi M, Widdicombe J. Respiratory expulsive efforts evoked by maximal lung emptying. *Chest* 2011: 140(3): 690-696.
231. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002: 166(4): 518-624.
232. Steier J, Kaul S, Seymour J, Jolley C, Rafferty G, Man W, Luo YM, Roughton M, Polkey MI, Moxham J. The value of multiple tests of respiratory muscle strength. *Thorax* 2007: 62(11): 975-980.
233. Hebbard GS, Reid K, Sun WM, Horowitz M, Dent J. Postural changes in proximal gastric volume and pressure measured using a gastric barostat. *Neurogastroenterol Motil* 1995: 7(3): 169-174.
234. Vanderstappen G, Texter EC, Jr. Response of the physiologic gastroesophageal sphincter to increased intra-abdominal pressure. *J Clin Invest* 1964: 43: 1856-1868.
235. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved technique for estimating pleural pressure from esophageal balloons. *J Appl Physiol* 1964: 19(2): 207-211.
236. Knudson RJ, Mead J, Knudson DE. Contribution of airway collapse to supramaximal expiratory flows. *J Appl Physiol* 1974: 36(6): 653-667.
237. Sharpey-Schafer EP. Effects of coughing on intrathoracic pressure, arterial pressure and peripheral blood flow. *J Physiol (Lond)* 1953: 122(2): 351-357.
238. Kelsall A, Houghton LA, Jones H, Decalmer S, McGuinness K, Smith JA. A Novel Approach to Studying the Relationship Between Subjective and Objective Measures of Cough. *Chest* 2011: 139(3): 569-575.

239. Ferris BG, Mead J, Frank NR. Effect of body position on esophageal pressure and measurement of pulmonary compliance. *J Appl Physiol* 1959: 14(4): 521-524.
240. Murty GE, Lancaster P, Kelly PJ. Cough intensity in patients with a vocal cord palsy. *Clinical Otolaryngology & Allied Sciences* 1991: 16(3): 248-251.
241. Goldsmith WT, Mahmoud AM, Reynolds JS, McKinney WG, Afshari AA, Abaza AA, Frazer DG. A system for recording high fidelity cough sound and airflow characteristics. *Ann Biomed Eng* 2010: 38(2): 469-477.
242. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005: 26(2): 319-338.
243. British Thoracic S. Guidelines for the measurement of respiratory function. *Respir Med* 1994: 88(3): 165-194.
244. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993: 16: 5-40.
245. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994: 47(1): 81-87.
246. Gallagher EJ. Nasogastric tubes: hard to swallow. *Ann Emerg Med* 2004: 44(2): 138-141.
247. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Respir Dis* 1982: 126(5): 788-791.
248. Mead J, McIlroy MB, Selverstone NJ, Kriete BC. Measurement of intraesophageal pressure. *J Appl Physiol* 1955: 7(5): 491-495.
249. Beardsmore CS, Helms P, Stocks J, Hatch DJ, Silverman M. Improved esophageal balloon technique for use in infants. *J Appl Physiol* 1980: 49(4): 735-742.
250. Jackson AC, Vinegar A. A technique for measuring frequency response of pressure, volume, and flow transducers. *J Appl Physiol* 1979: 47(2): 462-467.
251. Sykes K, Vickers MD, Hull CJ. Principles of Clinical Measurement. Blackwell Scientific, 1981.
252. Ojeaburu J, Banjamin SB. Normal esophageal physiology. *In:* Dimarino AJ, Benjamin SB, eds. Gastrointestinal disease An endoscopic approach. Slack Inc., New Jersey, 2002; pp. 173-190.
253. Pedersen OF, Rasmussen TR, Kjaergaard SK, Miller MR, Quanjer PH. Frequency response of variable orifice type peak flow meters: requirements and testing. *Eur Respir J* 1995: 8(5): 849-855.
254. Ives JC, Wigglesworth JK. Sampling rate effects on surface EMG timing and amplitude measures. *Clinical Biomechanics* 2003: 18(6): 543-552.
255. Man WD-C, Moxham J, Polkey MI. Magnetic stimulation for the measurement of respiratory and skeletal muscle function. *Eur Respir J* 2004: 24(5): 846-860.
256. Wragg S, Aquilina R, Moran J, Ridding M, Hamnegard C, Fearn T, Green M, Moxham J. Comparison of cervical magnetic stimulation and bilateral percutaneous electrical

stimulation of the phrenic nerves in normal subjects. *Eur Respir J* 1994: 7(10): 1788-1792.

257. Polkey MI, Luo Y, Guleria R, Hamnegard CH, Green M, Moxham J. Functional magnetic stimulation of the abdominal muscles in humans. *Am J Respir Crit Care Med* 1999: 160(2): 513-522.
258. Taylor BJ, Romer LM. Effect of expiratory resistive loading on inspiratory and expiratory muscle fatigue. *Respiratory physiology & neurobiology* 2009: 166(3): 164-174.
259. Luo Y, Johnson L, Polkey M, Harris M, Lyall R, Green M, Moxham J. Diaphragm electromyogram measured with unilateral magnetic stimulation. *Eur Respir J* 1999: 13(2): 385-390.
260. Hashimoto Y, Murata A, Mikami M, Nakamura S, Yamanaka E, Kudoh S. Influence of the rheological properties of airway mucus on cough sound generation. *Respirology* 2003: 8(1): 45-51.
261. Midgren B, Hansson L, Karlsson JA, Simonsson BG, Persson CG. Capsaicin-induced cough in humans. *Am Rev Respir Dis* 1992: 146(2): 347-351.
262. Dicpinigaitis PV. Short- and long-term reproducibility of capsaicin cough challenge testing. *Pulm Pharmacol Ther* 2003: 16(1): 61-65.
263. Dicpinigaitis PV, Alva RV. Safety of capsaicin cough challenge testing. *Chest* 2005: 128(1): 196-202.
264. Fujimura M, Kamio Y, Hashimoto T, Matsuda T. Cough receptor sensitivity and bronchial responsiveness in patients with only chronic nonproductive cough: in view of effect of bronchodilator therapy. *J Asthma* 1994: 31(6): 463-472.
265. Kopec SE, DeBellis RJ, Irwin RS. Chemical analysis of freshly prepared and stored capsaicin solutions: implications for tussigenic challenges. *Pulm Pharmacol Ther* 2002: 15(6): 529-534.
266. Yamanda S, Ebihara S, Ebihara T, Yamasaki M, Asamura T, Asada M, Une K, Arai H. Impaired urge-to-cough in elderly patients with aspiration pneumonia. *Cough* 2008: 4: 11.
267. Irwin RSS. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest* 1998: 114(2): 133-181.
268. Bolser DC. Cough Suppressant and Pharmacologic Protussive Therapy. *Chest* 2006: 129(1 suppl): 238S-249S.
269. Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID. Induced sputum inflammatory mediator concentrations in chronic cough. *American Journal of Respiratory and Critical Care Medicine* 2004: 169(1): 15-19.
270. Lee KK, Matos S, Evans DH, Pavord ID, Birring SS. Changes In Cough Frequency, Cough Severity And Quality Of Life In Acute Cough [abstract]. *Am J Respir Crit Care Med* 2012: May 2012; 185: A5850.
271. Kuhn JJ, Hendley JO, Adams KF, Clark JW, Gwaltney JM. Antitussive effect of guaifenesin in young adults with natural colds. Objective and subjective assessment. *Chest* 1982: 82(6): 713-718.
272. Snapinn SM, Jiang Q. Responder analyses and the assessment of a clinically relevant treatment effect. *Trials* 2007: 8: 31.

273. French CT, Fletcher KE, Irwin RS. A comparison of gender differences in health-related quality of life in acute and chronic coughers. *Chest* 2005: 127(6): 1991-1998.
274. Yousaf N, Monteiro W, Matos S, Birring SS, Pavord ID. Cough frequency in health and disease. *Eur Respir J* 2012: (In press).
275. Fletcher KE, French CT, Irwin RS, Corapi KM, Norman GR. A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure. *J Clin Epidemiol* 2010: 63(10): 1123-1131.
276. Morice AH, Fontana GA, Sovijarvi ARA, Pistolesi M, Chung KF, Widdicombe J, O'Connell F, Geppetti P, Gronke L, De Jongste J, Belvisi M, Dicpinigaitis P, Fischer A, McGarvey L, Fokkens WJ, Kastelik J, Force ERST. The diagnosis and management of chronic cough. *Eur Respir J* 2004: 24(3): 481-492.
277. Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dicpinigaitis PV, Kastelik JA, McGarvey LP, Smith JA, Tatar M, Widdicombe J, European Respiratory Society. ERS guidelines on the assessment of cough. *European Respiratory Journal* 2007: 29(6): 1256-1276.
278. Kelley K. Confidence Intervals for Standardized Effect Sizes: Theory, Application, and Implementation. *Journal of Statistical Software* 2007: 20(i08).
279. Kelsall A, Decalmer S, McGuinness K, Woodcock A, Smith JA. Sex differences and predictors of objective cough frequency in chronic cough. *Thorax* 2009: 64(5): 393-398.
280. Chung KF. Assessment and measurement of cough: the value of new tools. *Pulm Pharmacol Ther* 2002: 15(3): 267-272.
281. Lee KK, Matos S, Evans DH, White P, Pavord ID, Birring SS. A Longitudinal Assessment of Acute Cough. *Am J Respir Crit Care Med* 2013: 187(9): 991-997.
282. Morice AH. Rebuttal: cough is an expiratory sound. *Lung* 2008: 186 Suppl 1: S7-9.
283. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. *Thorax* 1984: 39(7): 535-538.
284. McBain RA, Boswell-Ruys CL, Lee BB, Gandevia SC, Butler JE. Abdominal Muscle Training Can Enhance Cough After Spinal Cord Injury. *Neurorehabilitation and Neural Repair* 2013.
285. Hegland KW, Troche MS, Davenport PW. Cough expired volume and airflow rates during sequential induced cough. *Frontiers in Physiology* 2013: 4.
286. Olia PM, Sestini P, Vagliasindi M. Acoustic parameters of voluntary cough in healthy non-smoking subjects. *Respirology* 2000: 5(3): 271-275.
287. Freestone C, Eccles R, Morris S, Jawad MS. Assessment of the antitussive efficacy of codeine using cough sound pressure levels as a means of measuring cough. *Pulm Pharmacol* 1996: 9(5-6): 365.
288. Alimohamed S, Prosser K, Weerasuriya C, Iles R, Cameron J, Lasenby J, Fogarty C. Validating structured light plethysmography (SLP) as a non-invasive method of measuring lung function when compared to Spirometry [Abstract]. *Thorax* 2011: 66(Suppl 4): A121.
289. Layton AM, Moran SL, Garber CE, Armstrong HF, Basner RC, Thomashow BM, Bartels MN. Optoelectronic plethysmography compared to spirometry during maximal exercise. *Respiratory physiology & neurobiology* 2013: 185(2): 362-368.

10 Appendices

Appendix 1 Supporting data for validation of pressure volume characteristics of balloon catheter system

Volume of air added to balloon (ml)	Balloon pressure (cmH_2O)
0.0	-2.8
0.1	-0.1
0.2	0.0
0.3	0.0
0.4	0.0
0.5	0.0
0.6	0.0
0.7	0.0
0.8	0.0
0.9	0.0
1.0	0.0
1.1	0.1
1.2	0.1
1.3	0.1
1.4	0.1
1.5	0.2
1.6	0.2
1.7	0.2
1.8	0.3
1.9	0.3
2.0	0.4
2.1	0.6
2.2	0.8
2.3	1.1
2.4	1.2
2.5	1.6
2.6	1.6
2.7	2.0
2.8	2.7
2.9	3.0
3.0	3.5
3.1	4.2
3.2	5.3

Data shown from single experiment performed under laboratory conditions.

Appendix 2 Supporting data for validation of linearity of mouth pressure transducer system

Applied pressure (cmH_2O)	System output (V)
-250	-4.62
-225	-4.15
-200	-3.66
-175	-3.22
-150	-2.76
-125	-2.27
-100	-1.85
-75	-1.40
-50	-0.94
-25	-0.46
0	0
25	0.45
50	0.91
75	1.37
100	1.82
125	2.29
150	2.76
175	3.22
200	3.69
225	4.16
250	4.63

Data shown from single experiment performed under laboratory conditions.

Appendix 3 Supporting data for validation of linearity of oesophageal balloon catheter system

Applied pressure (cmH_2O)	System output (V)
-200	-2.62
-190	-2.49
-180	-2.36
-170	-2.22
-160	-2.10
-150	-1.98
-140	-1.84
-130	-1.72
-120	-1.58
-110	-1.44
-100	-1.34
-90	-1.22
-80	-1.07
-70	-0.94
-60	-0.80
-50	-0.68
-40	-0.54
-30	-0.42
-20	-0.29
-10	-0.13
0	0
10	0.15
21	0.29
30	0.42
40	0.55
51	0.69
61	0.82
70	0.94
81	1.10
90	1.21
99	1.32
108	1.44
117	1.57
126	1.68
138	1.83
149	1.97
159	2.11
171	2.26
180	2.37
191	2.52
199	2.62
208	2.73
216	2.81
226	2.92
235	2.98
250	3.04

Data shown from single experiment performed under laboratory conditions.

Appendix 4 Supporting data for validation of linearity of gastric balloon catheter system

Applied pressure (cmH_2O)	System output (V)
-205	-1.68
-194	-1.65
-181	-1.60
-173	-1.57
-160	-1.51
-148	-1.43
-138	-1.38
-130	-1.33
-120	-1.27
-109	-1.21
-100	-1.14
-91	-1.07
-79	-0.97
-70	-0.88
-59	-0.75
-50	-0.65
-40	-0.53
-30	-0.39
-20	-0.26
-11	-0.14
0	0
10	0.16
20	0.29
30	0.42
40	0.56
50	0.68
60	0.81
70	0.94
80	1.08
90	1.21
100	1.34
110	1.47
120	1.59
131	1.75
140	1.86
149	1.98
161	2.13
171	2.26
180	2.38
190	2.50
197	2.60
200	2.63
215	2.82
225	2.96
235	3.08
255	3.35

Data shown from single experiment performed under laboratory conditions.

Appendix 5 Supporting data for validation of linearity of pneumotachograph system

Applied flow rate (L/min)	System output (V)
-700	-2.25
-600	-1.88
-500	-1.55
-400	-1.23
-300	-0.90
-200	-0.60
-100	-0.31
0	0
100	0.30
200	0.59
300	0.89
400	1.20
500	1.52
600	1.86
700	2.21

Data shown from single experiment performed under laboratory conditions.

Appendix 6 Supporting data for validation of linearity of pneumotachograph system following capsaicin nebulisation

Applied flow rate (L/min)	System output (V)
-700	-0.59
-600	-0.50
-500	-0.40
-400	-0.31
-300	-0.22
-200	-0.15
-100	-0.07
0	0
100	0.07
200	0.13
300	0.21
400	0.28
500	0.35
600	0.44
700	0.51

Data shown from single experiment performed under laboratory conditions.

Appendix 7 Supporting data for validation of supramaximality of lower thoracic nerve root magnetic stimulation

Power output of magnetic stimulator (%)	CMAP amplitude (mV)
30	0.17 ± 0.06
40	0.84 ± 0.41
50	0.66 ± 0.17
60	1.38 ± 0.34
70	1.17 ± 0.31
80	1.35 ± 0.28
90	1.85 ± 0.31
100	1.86 ± 0.29

Data acquired from patients with chronic cough and healthy controls and presented as mean ± SEM. CMAP: abdominal compound muscle action potential.

Acknowledgements

The work within this thesis is the culmination of a 4-year journey beginning in 2009 in the research laboratory at King's College Hospital. During that time, I faced many trials and tribulations that can only be appreciated by those who accompanied me along the way. It is with this in mind that I wish to acknowledge those, without whose help, it would not have been possible to complete this.

I must thank my supervisors, Dr Surinder Birring for the continuous guidance and motivation, and Professor John Moxham for his wisdom and inspiration. I am also grateful to Dr Sergio Matos, Professor David Evans and Dr Gerrard Rafferty for sharing their expertise in engineering and physiology, and to every patient and volunteer for his or her willingness, trust and participation in the studies.

To my colleagues and friends within the research laboratory, Alan Lunt, Amit Patel, Arietta Spinou, Bronwyn Connolly, Charlie Riley, Katie Ward and Vicky MacBean, I am indebted to you all for the discussions, debates and advice, but most of all for simply making the experience more enjoyable than one could have wished. I consider myself privileged to have shared my journey with you all. The memories will live long!

Finally, special thanks go to my fiancée, Emma, and all of my family for the unconditional support in everything that I do. This thesis is dedicated to my father, Tim Shing Lee.